FIG. 1

Summary of the current purification protocol

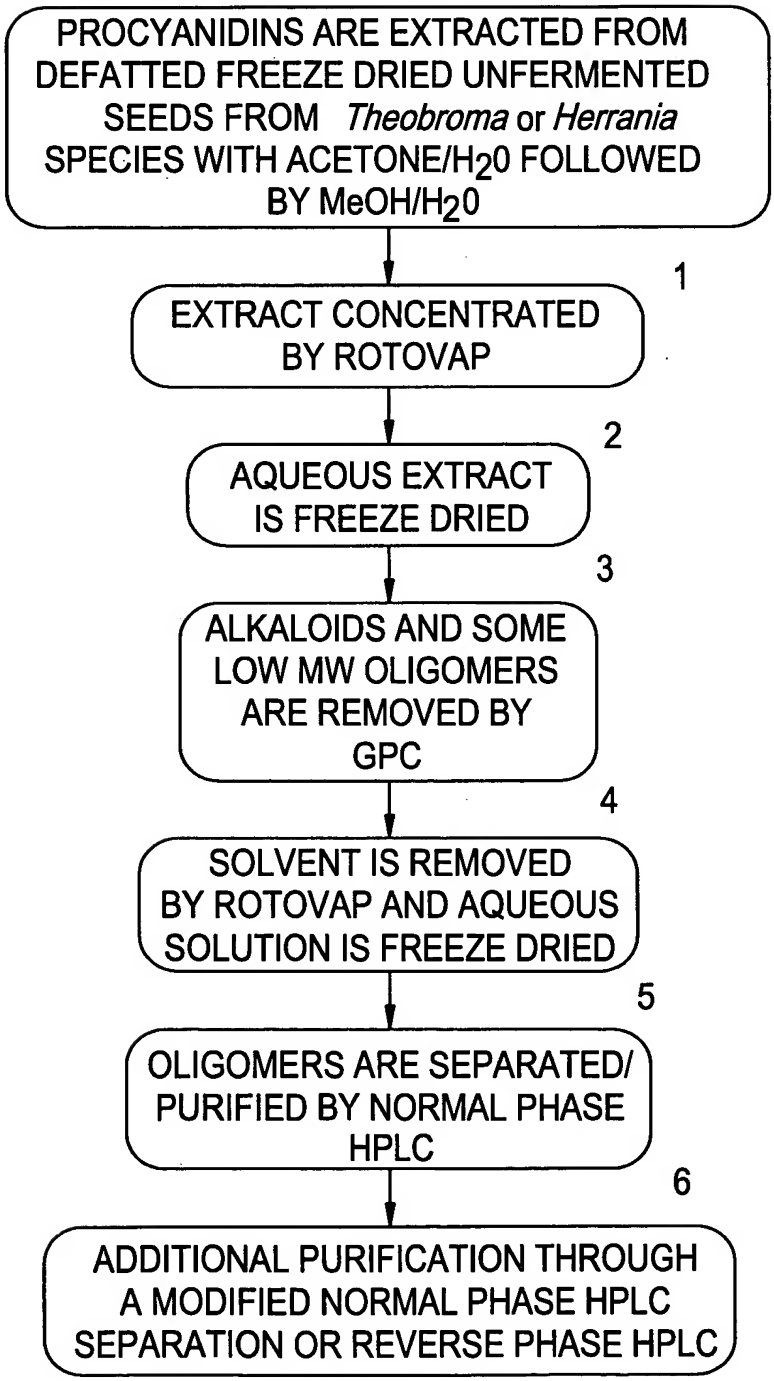


FIG. 2A

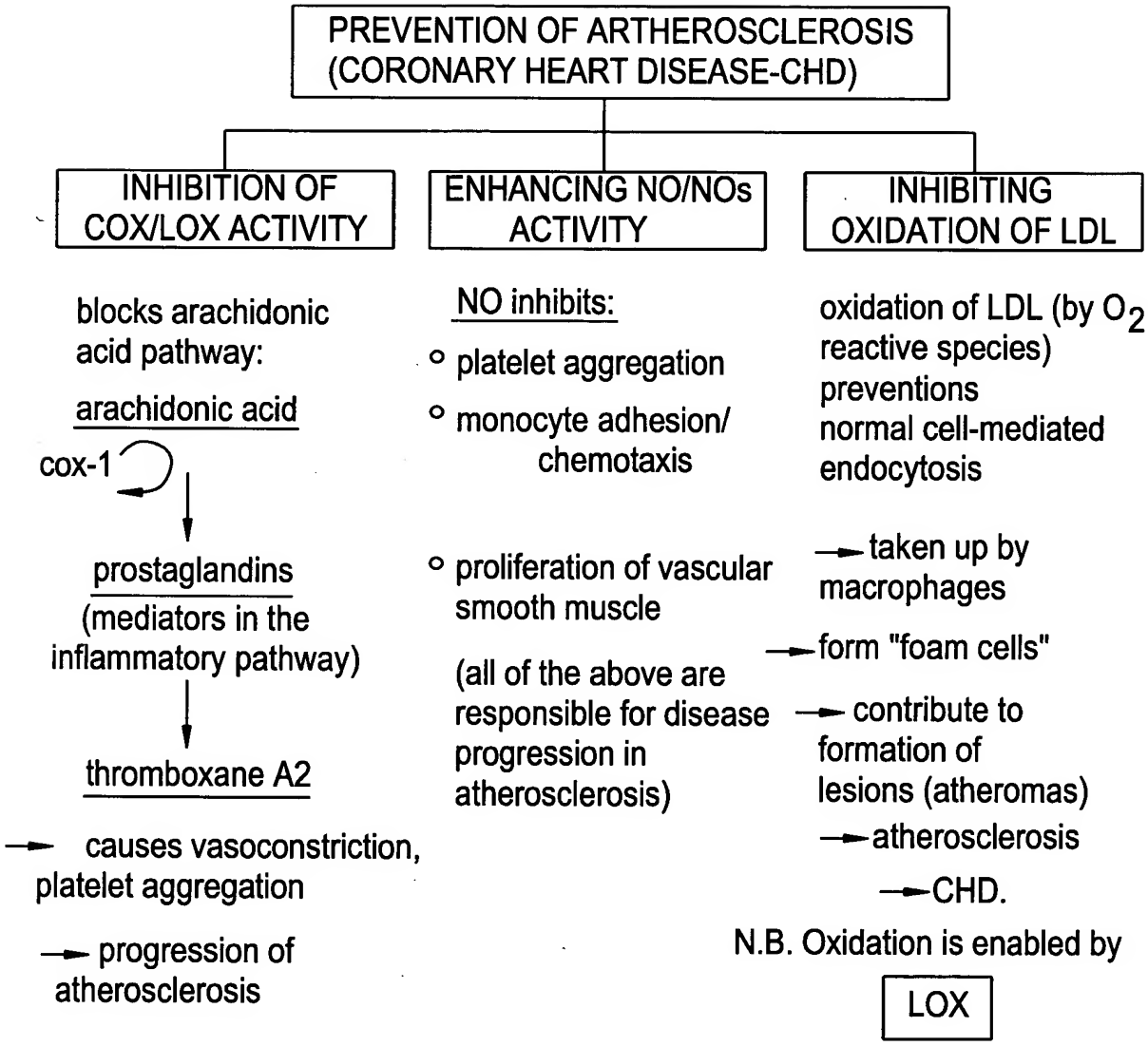


Chart showing the major contributing factors in the progression of Coronary Heart Disease (CHD) and how the activity of cocoa procyanidins contributes to the prevention of the progression of the disease state

FIG. 2B

The cocoa procyanidins induce the activity of NOS and therefore the resulting production NO, thereby enhancing the health benefits mediated by the activity of nitric oxide (NO).

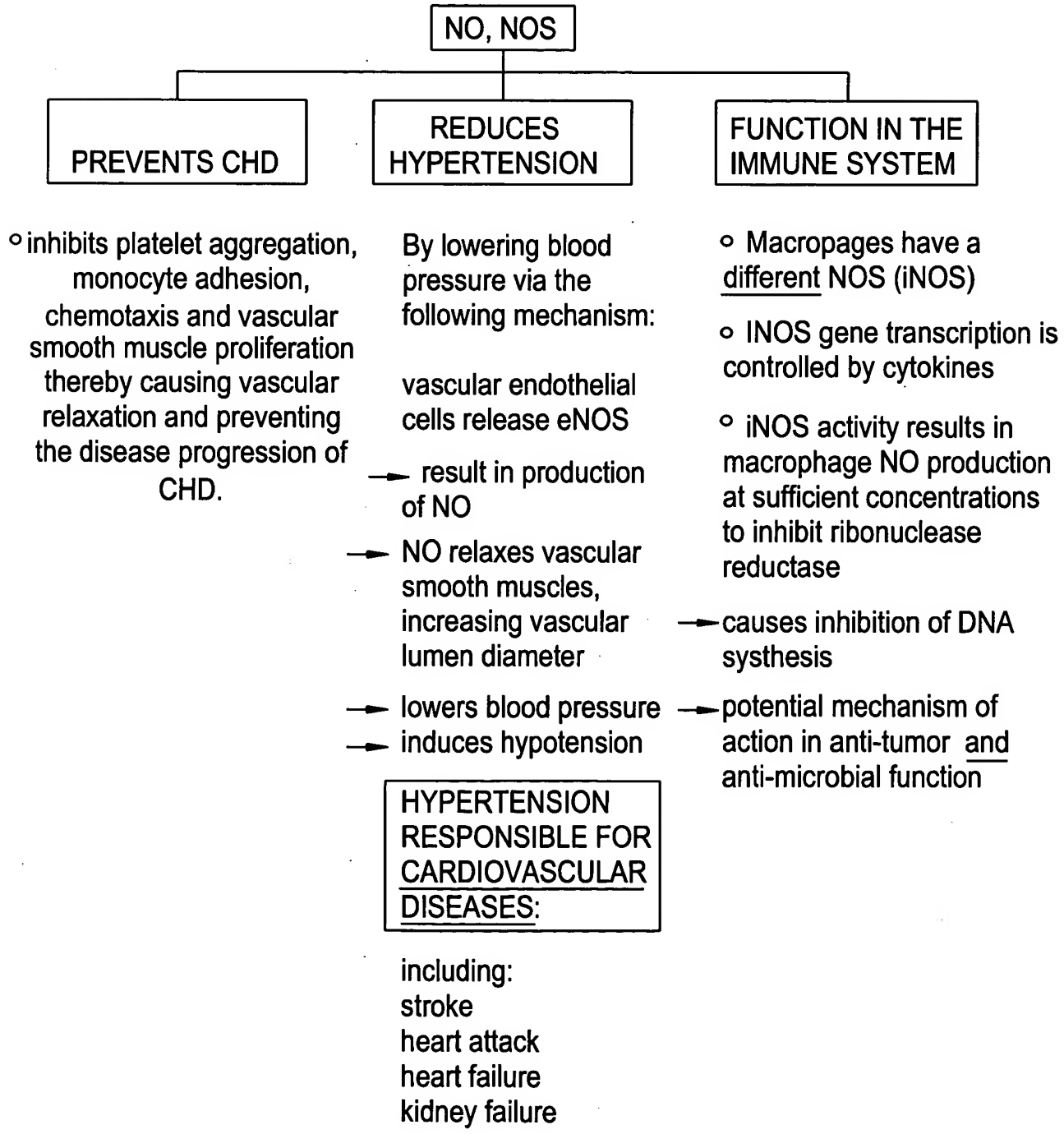
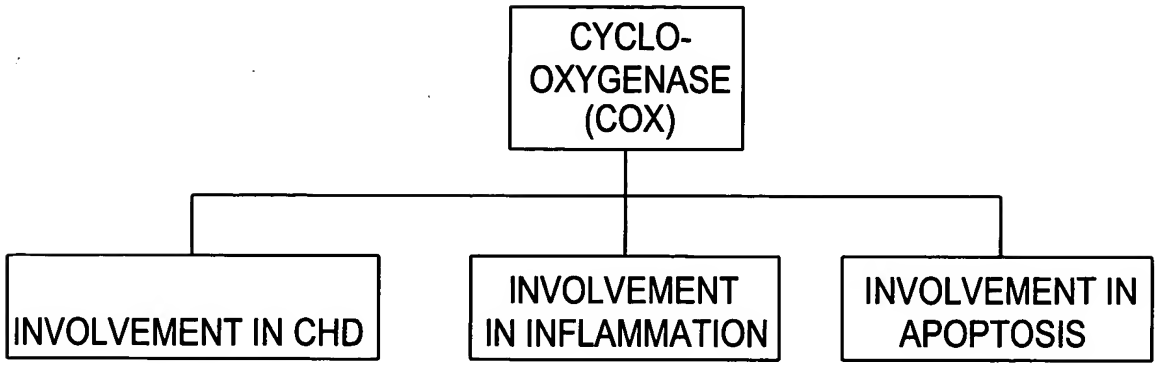


FIG. 2C



COX-1 is essential in the arachidonic acid pathway which results in the production of thromboxane.

→ thromboxane and prostaglandins which promote platelet aggregation and vasoconstriction

→ resulting in progression of atherosclerosis.

COX-1 is an essential enzyme in the inflammatory pathway, the penultimate products of which (the prostaglandins) are largely responsible for the inflammatory pathway, the results of which contribute to a variety of diseases including:

→ bowel disease, arthritis, edema, gingivitis/ peridontitis, etc.

COX-2 producing cells lines show enhanced expression of genes known to be involved in apoptosis:

→ potential putative mechanism of killing tumor cells.

The cocoa procyanidins inhibit the production of cyclo-oxygenase, thereby blocking the arachidonic acid pathway, which is responsible for the inflammatory response and the vasoconstrictive and platelet aggregating responses which contribute to the disease progression of CHD.

FIG. 3

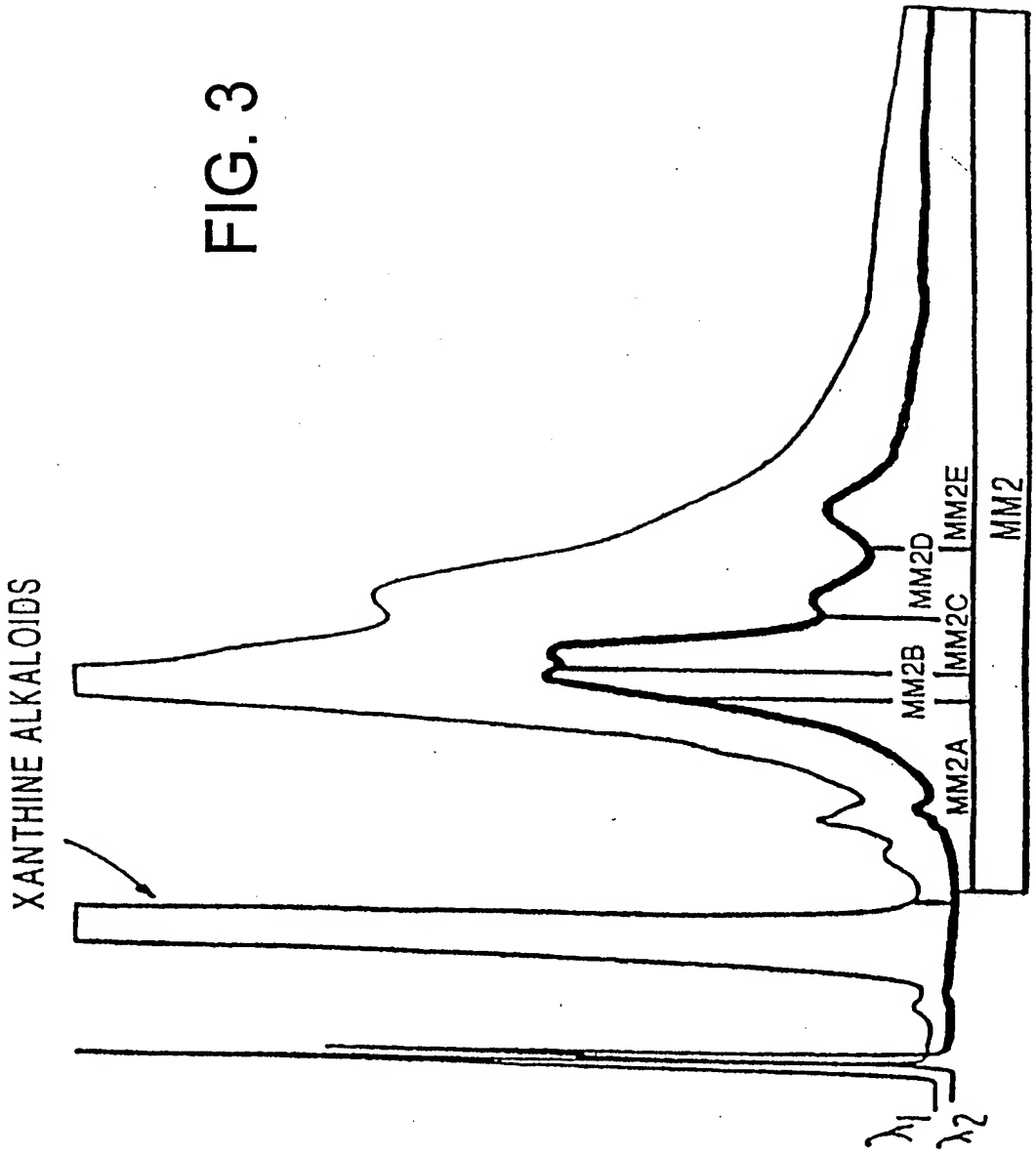


FIG. 4

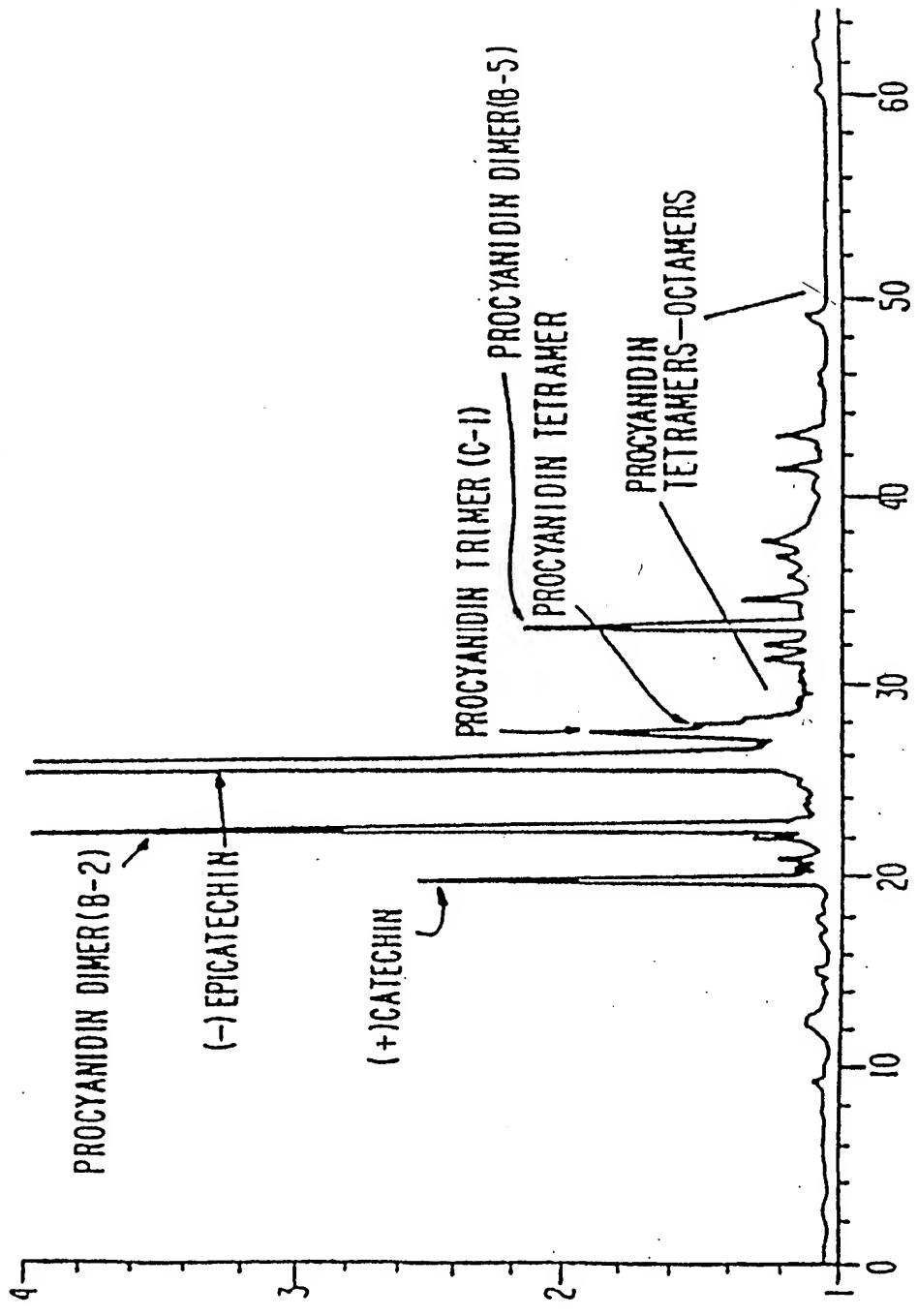

PROCYANIDIN DIMER(B-2)
(-) EPICATECHIN
(+)CATECHIN
PROCYANIDIN TRIMER (C-1)
PROCYANIDIN DIMER(B-5)
PROCYANIDIN TETRAMER
PROCYANIDIN TETRAMERS—OCTAMERS
4
3
2
1
0
10
20
30
40
50
60

FIG. 5

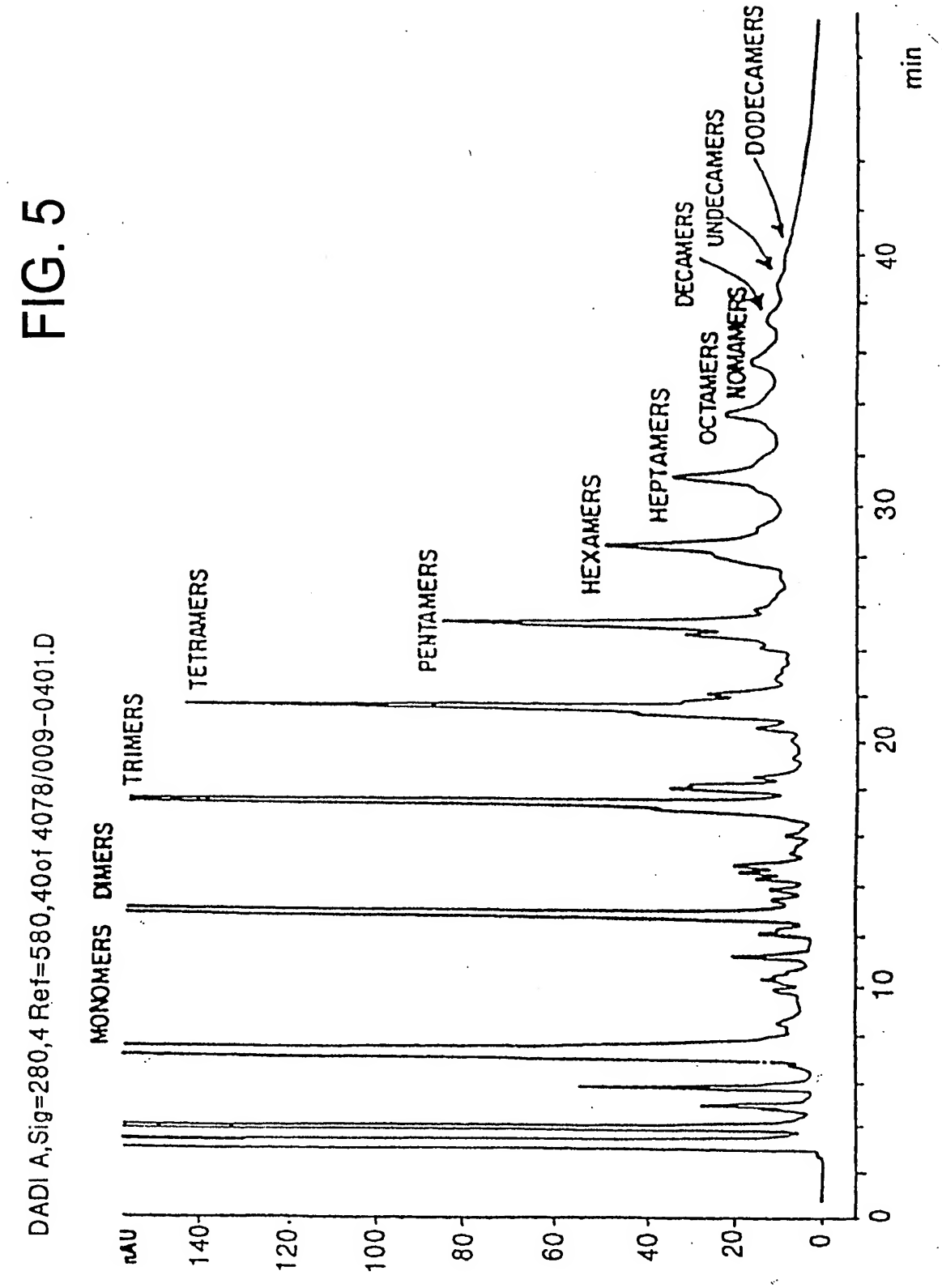

DAD1 A,Sig=280,4 Ref=580,40of 4078/009-0401.D
mAU
140
120
100
80
60
40
20
0
MONOMERS
DIMERS
TRIMERS
TETRAMERS
PENTAMERS
HEXAMERS
HEPTAMERS
OCTAMERS
NONAMERS
DECAMERS
UNDECAMERS
DODECAMERS
0
10
20
30
40
min

FIG. 6

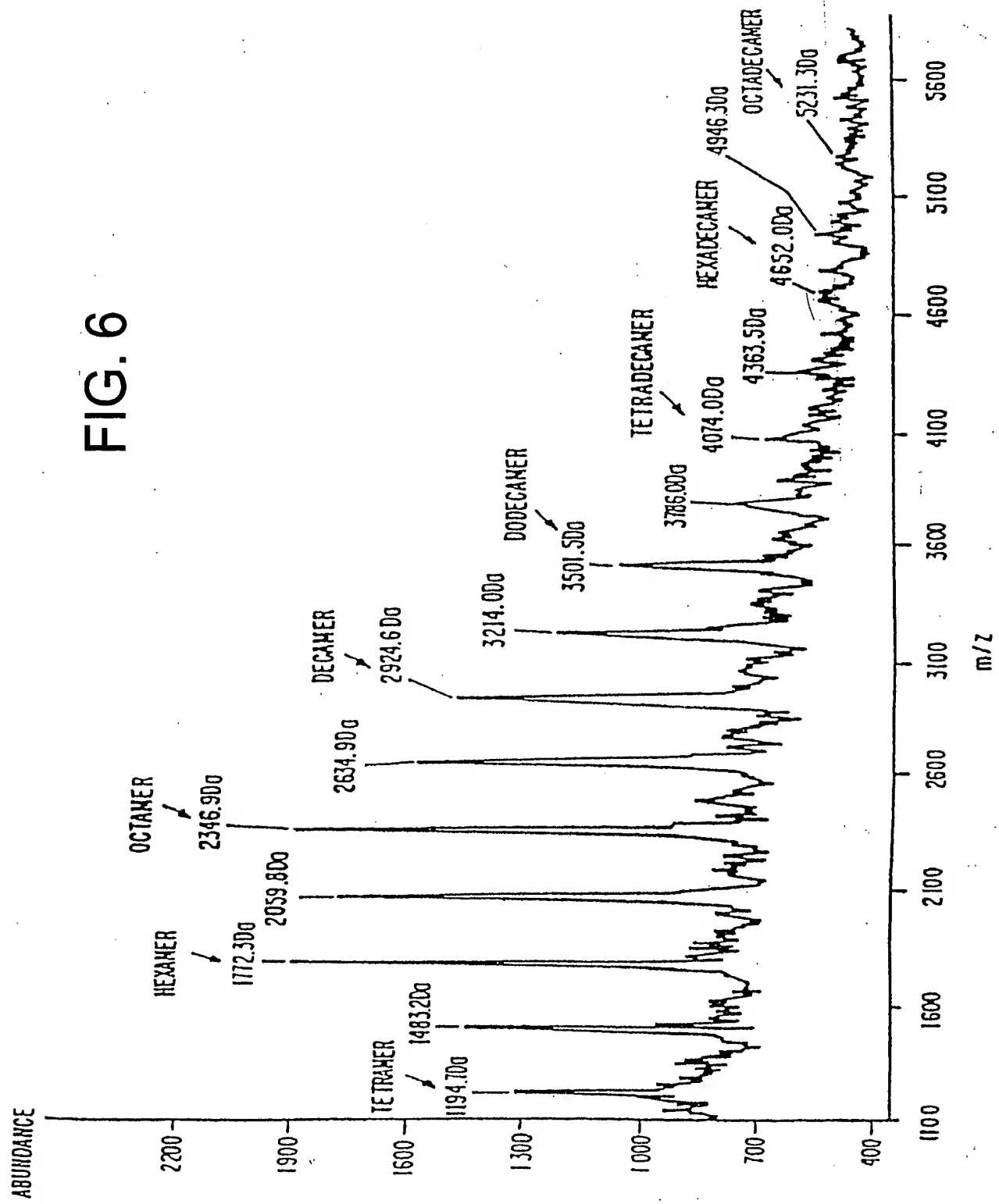

ABUNDANCE
2200
1900
1600
1300
1000
700
400
1100
1600
2100
2600
3100
3600
4100
4600
5100
5600
m/z
TETRAMER
1194.7Da
HEXAMER
1483.2Da
1772.3Da
OCTAMER
2059.8Da
2346.9Da
DECAMER
2634.9Da
2924.6Da
DODECAMER
3214.0Da
3501.5Da
TETRADECAMER
3786.0Da
4074.0Da
HEXADECAMER
4363.5Da
4652.0Da
OCTADECAMER
4946.3Da
5231.3Da

FIG. 7

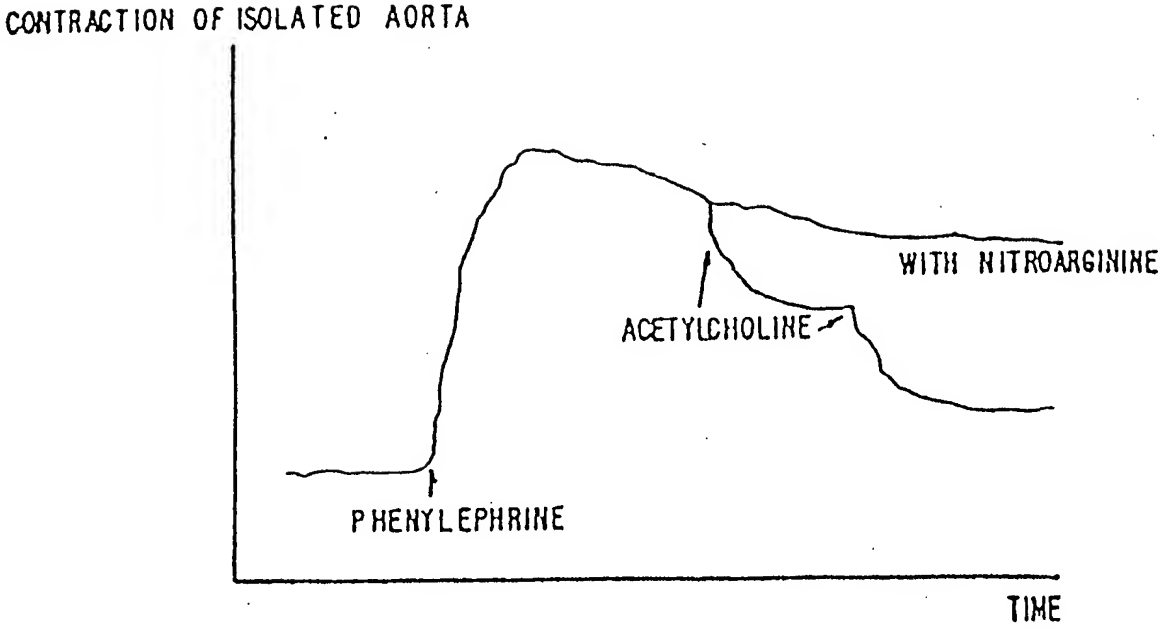
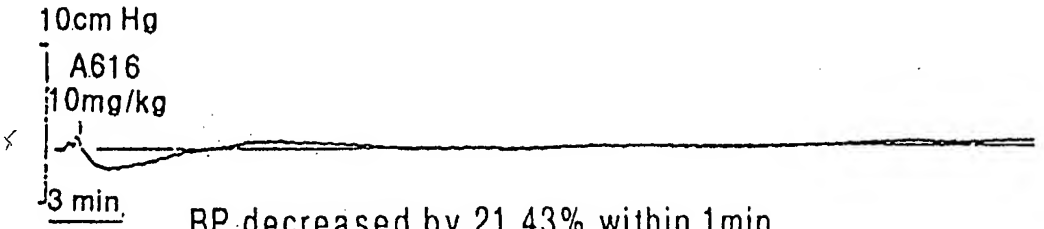

CONTRACTION OF ISOLATED AORTA
WITH NITROARGININE
ACETYLCHOLINE
PHENYLEPHRINE
TIME

FIG. 8A

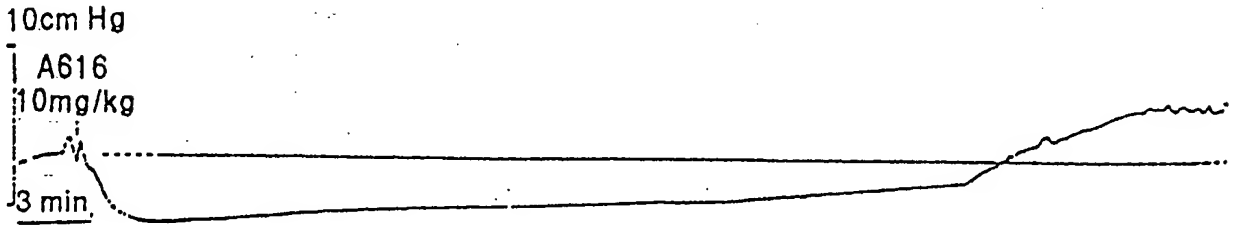
EFFECT OF COCOA PROCYANIDIN FRACTION A ON BLOOD PRESSURE



BP decreased by 21.43% within 1min
BP back to normal value after 1.5 min

FIG. 8B

EFFECT OF COCOA PROCYANIDIN FRACTION C ON BLOOD PRESSURE



BP decreased by 50.5% within 1 min
BP back to normal value after 5 min

REPLACEMENT SHEET

10/789,298

FIG. 9

EFFECT OF COCOA PROCYANIDIN FRACTIONS ON ARTERIAL BLOOD PRESSURE IN ANESTHESIZED GUINEA PIGS

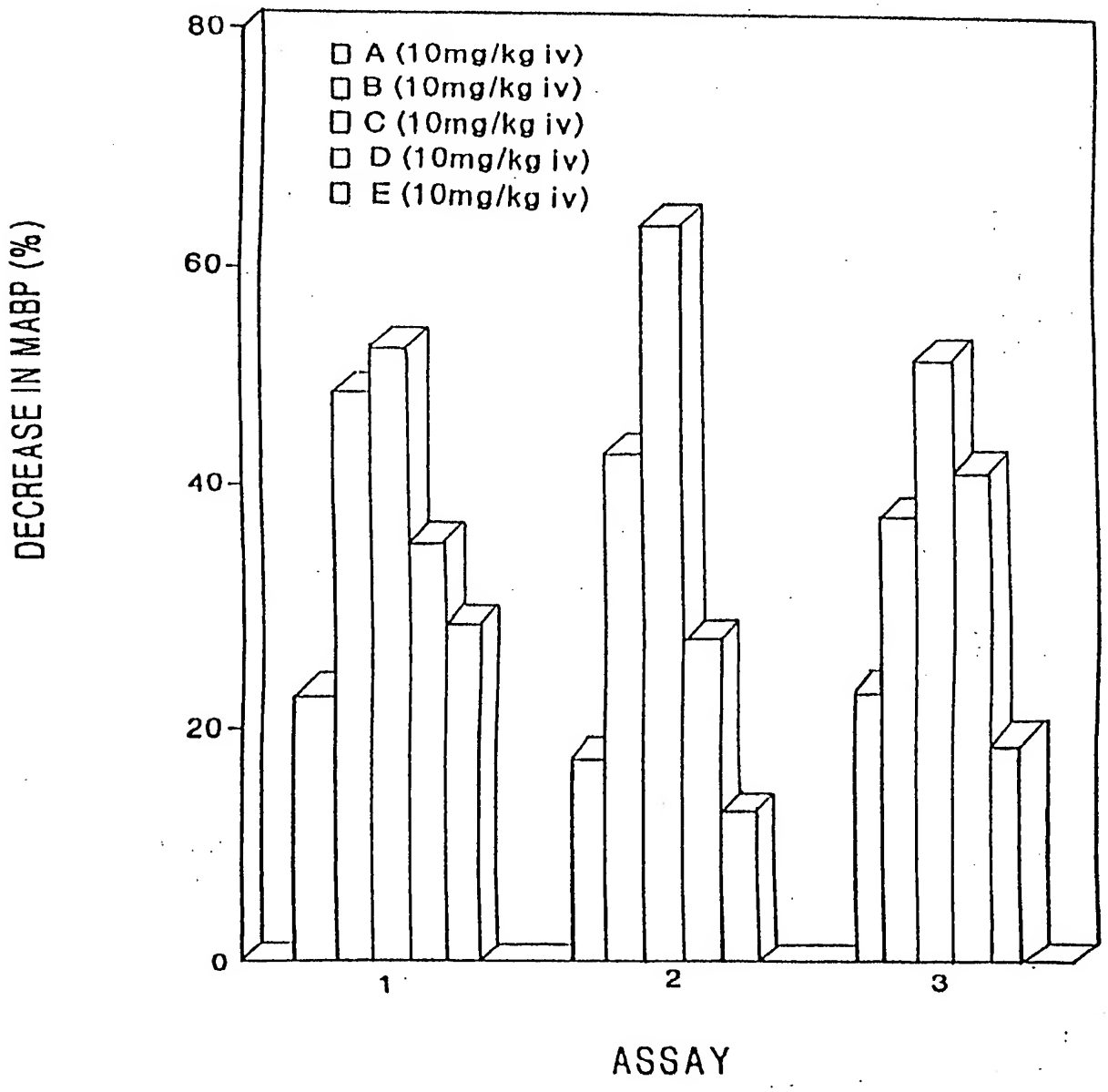


FIG. 10

EFFECT OF L-NMMA ON THE ALTERATIONS OF ARTERIAL BLOOD PRESSURE IN ANESTHESIZED GUINEA PIGS INDUCED BY COCOA PROCYANIDIN FRACTION C

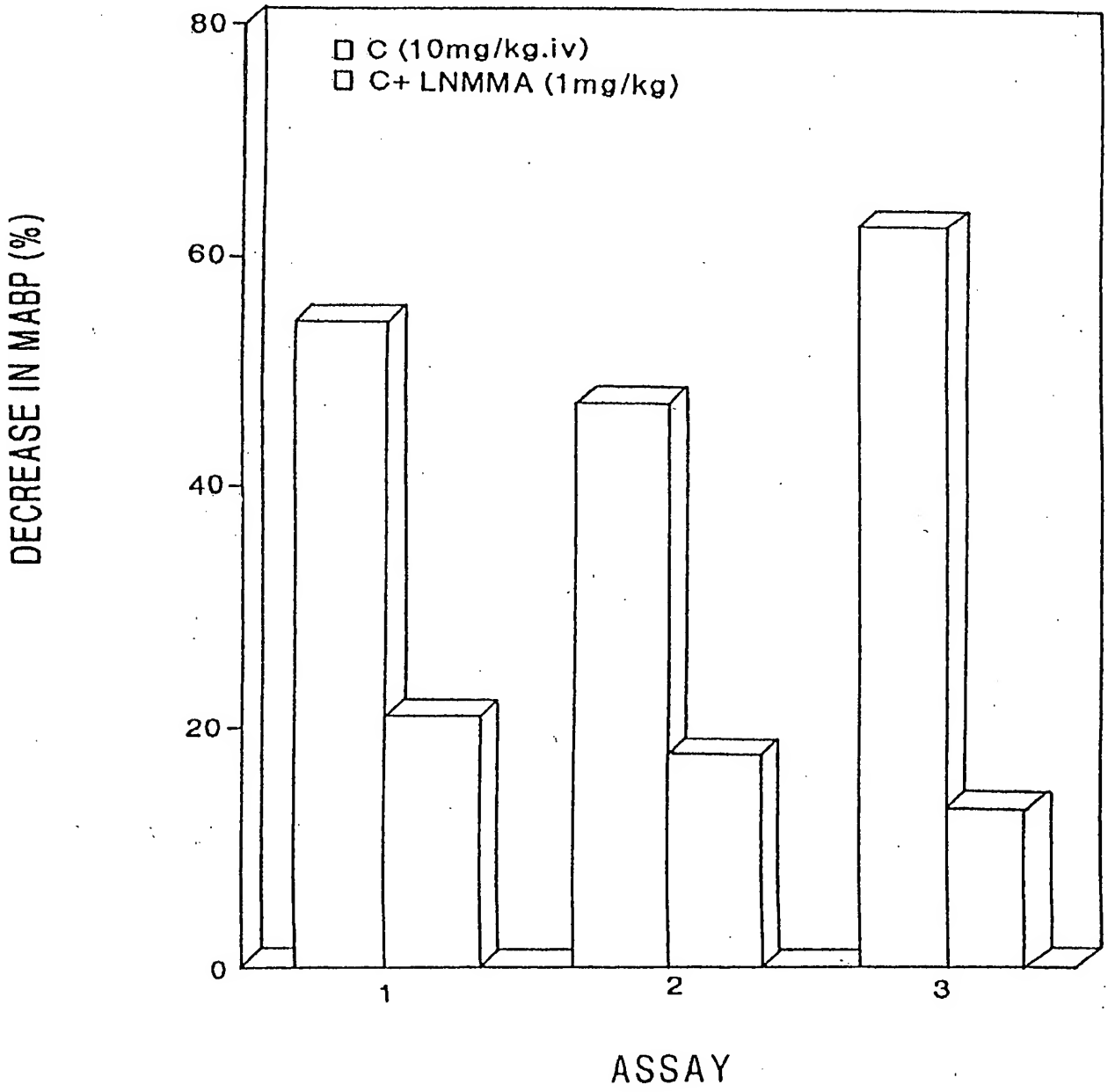


FIG. 11

EFFECT OF BRADYKININ ON NO PRODUCTION BY HUVEC

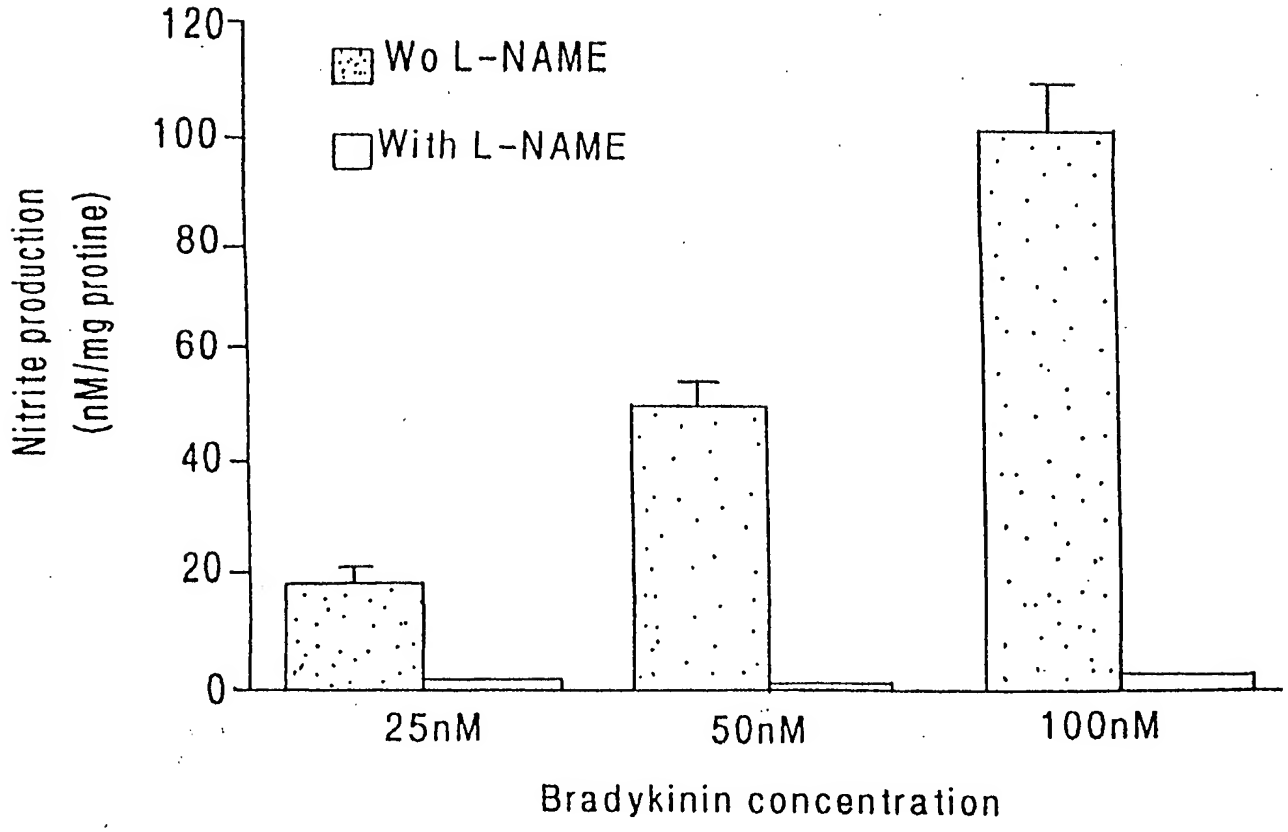


FIG. 12

EFFECT OF COCOA PROCYANIDIN FRACTIONS ON NO PRODUCTION BY HUVEC

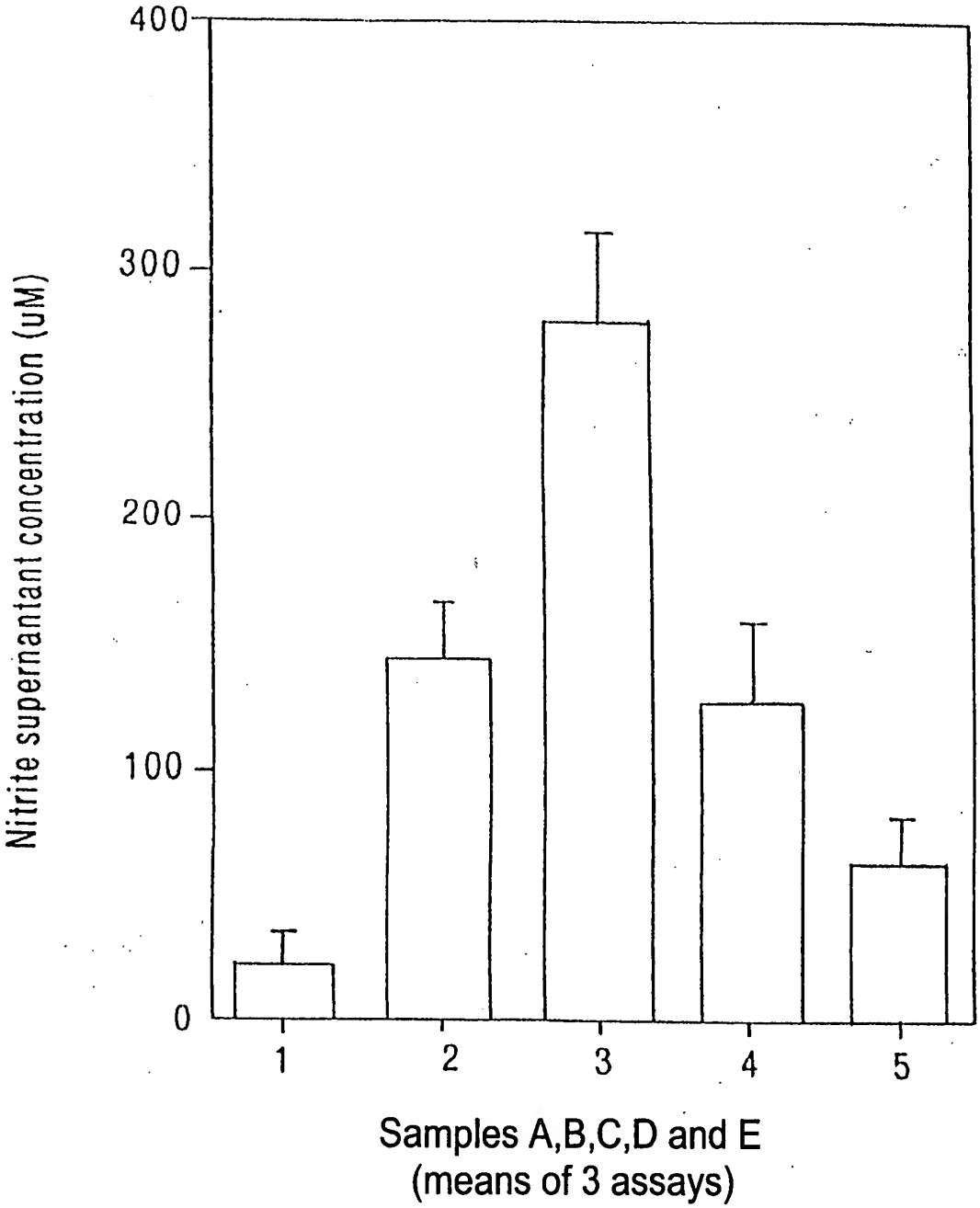


FIG. 13

Figure A:Effect of Cocoa Procyanidin Fractions on Macrophage NO Production

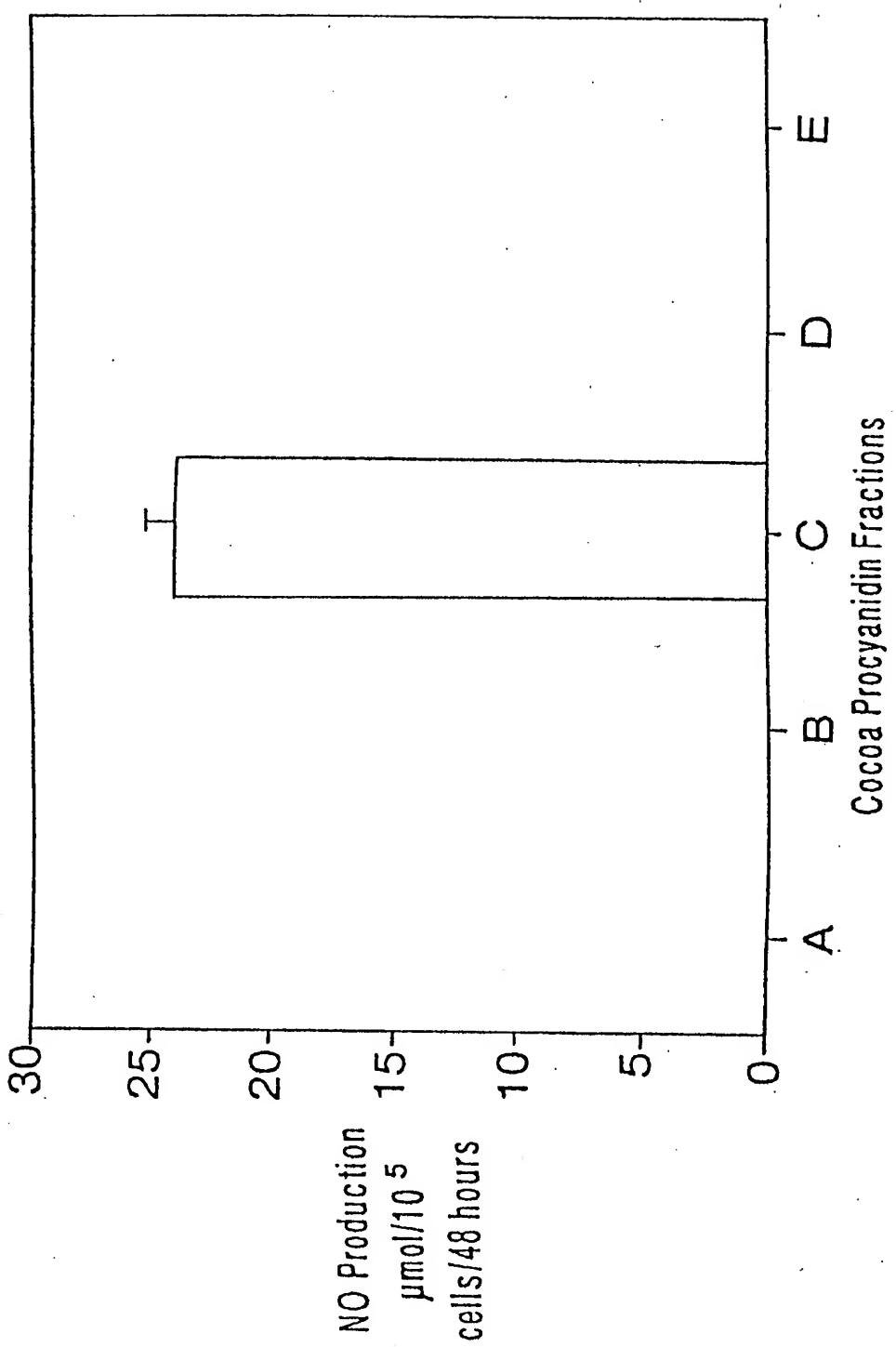


FIG. 14

Figure B:Effect of Cocoa Procyanidin Fractions on LPS Induced and γ-Interferon Primed Macrophages

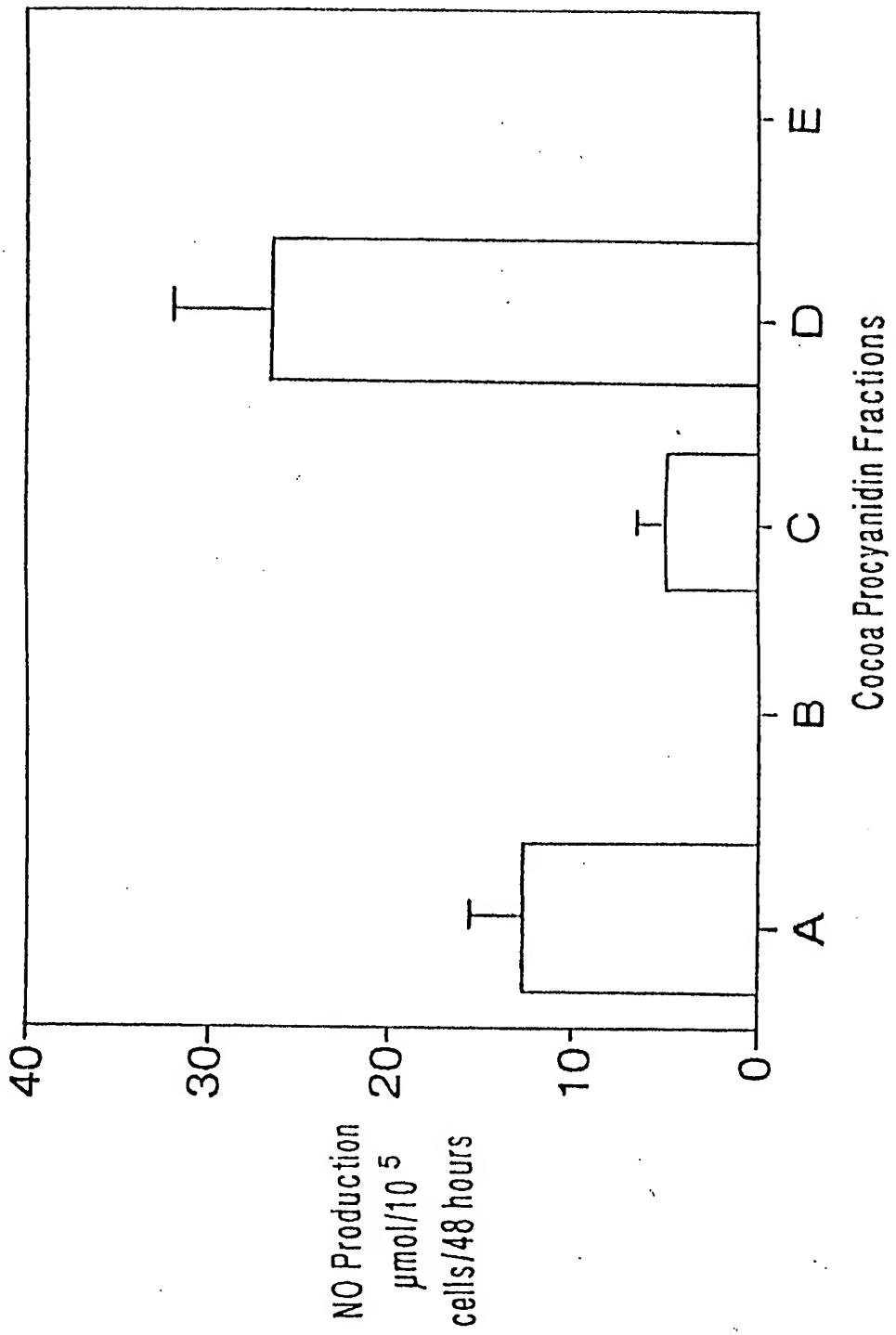


FIG. 15A

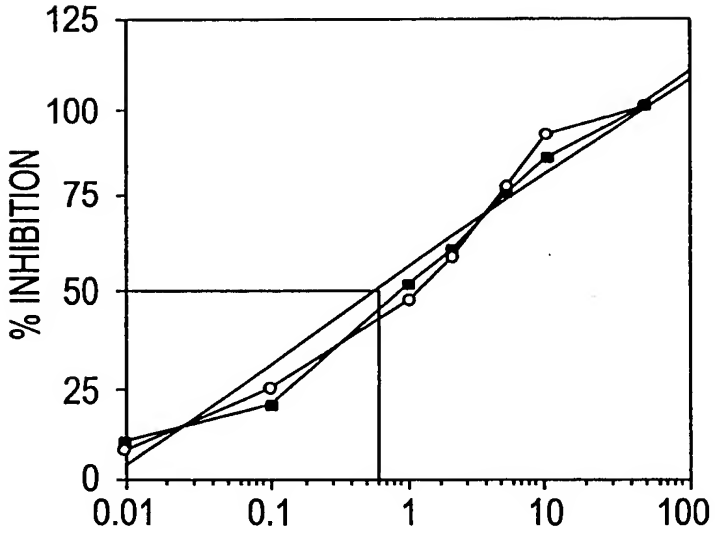


FIG. 15B

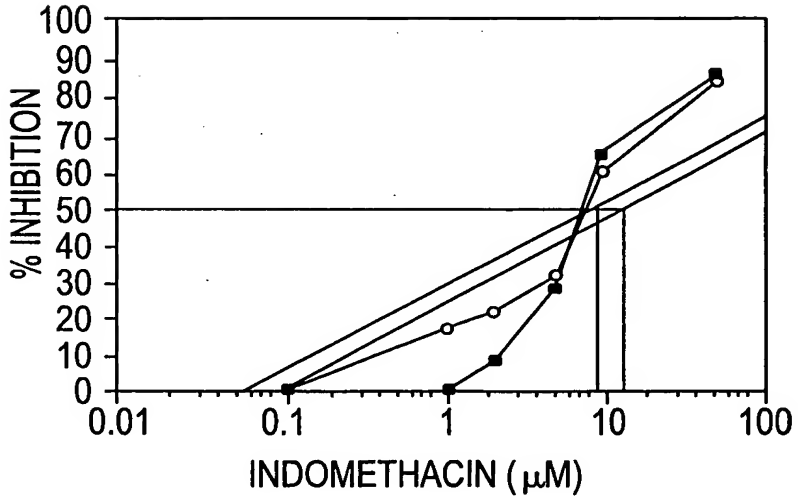
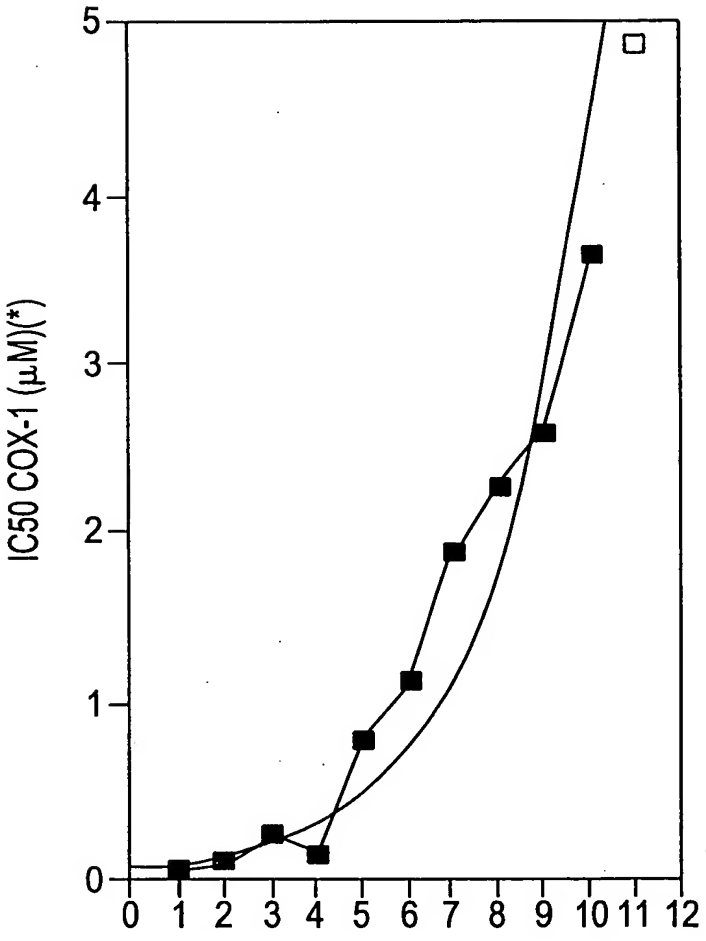
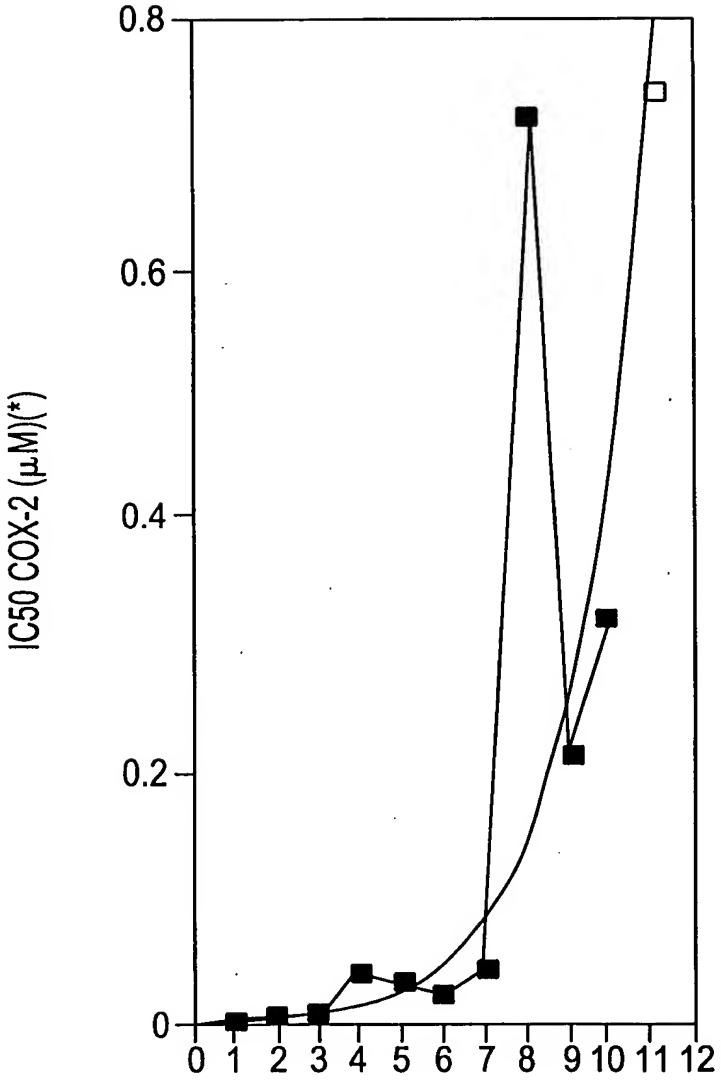


FIG. 16A



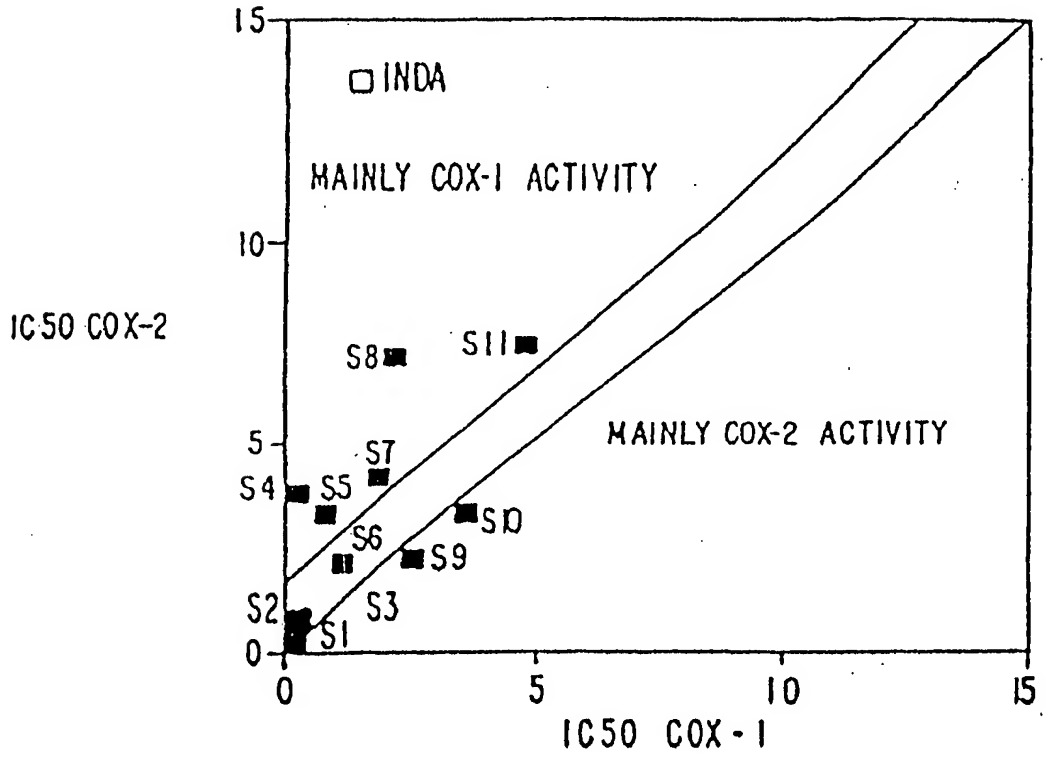
DEGREE OF POLYMERIZATION (SAMPLE #)
(*) WITH THE EXCEPTION OF SAMPLE S11 EXPRESSED AS mg/ml

FIG. 16B



(*) WITH THE EXCEPTION OF SAMPLE S11 EXPRESSED AS mg/ml

FIG. 17



(*) WITH THE EXEPTION OF SAMPLE S11

FIG. 18A

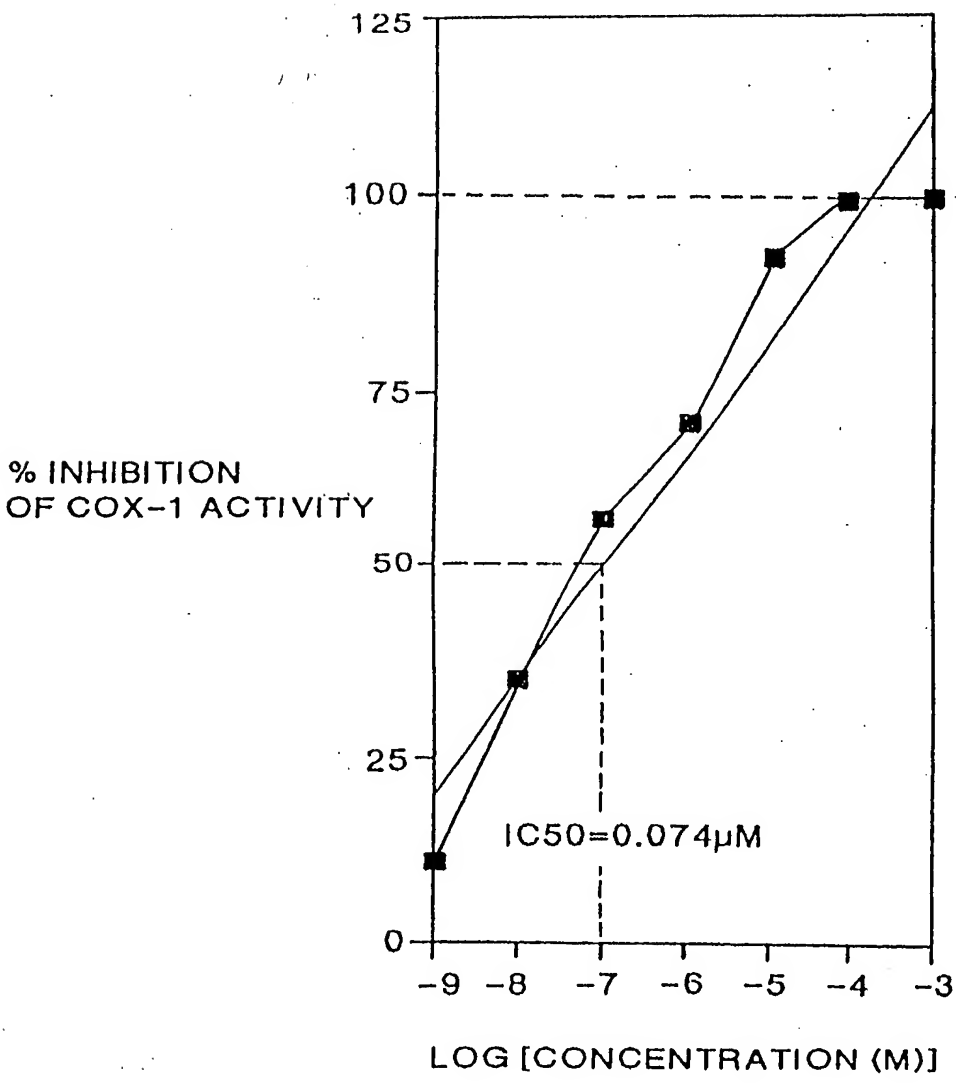

125
100
75
50
25
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=0.074μM
-9 -8 -7 -6 -5 -4 -3
LOG [CONCENTRATION (M)]

FIG. 18B

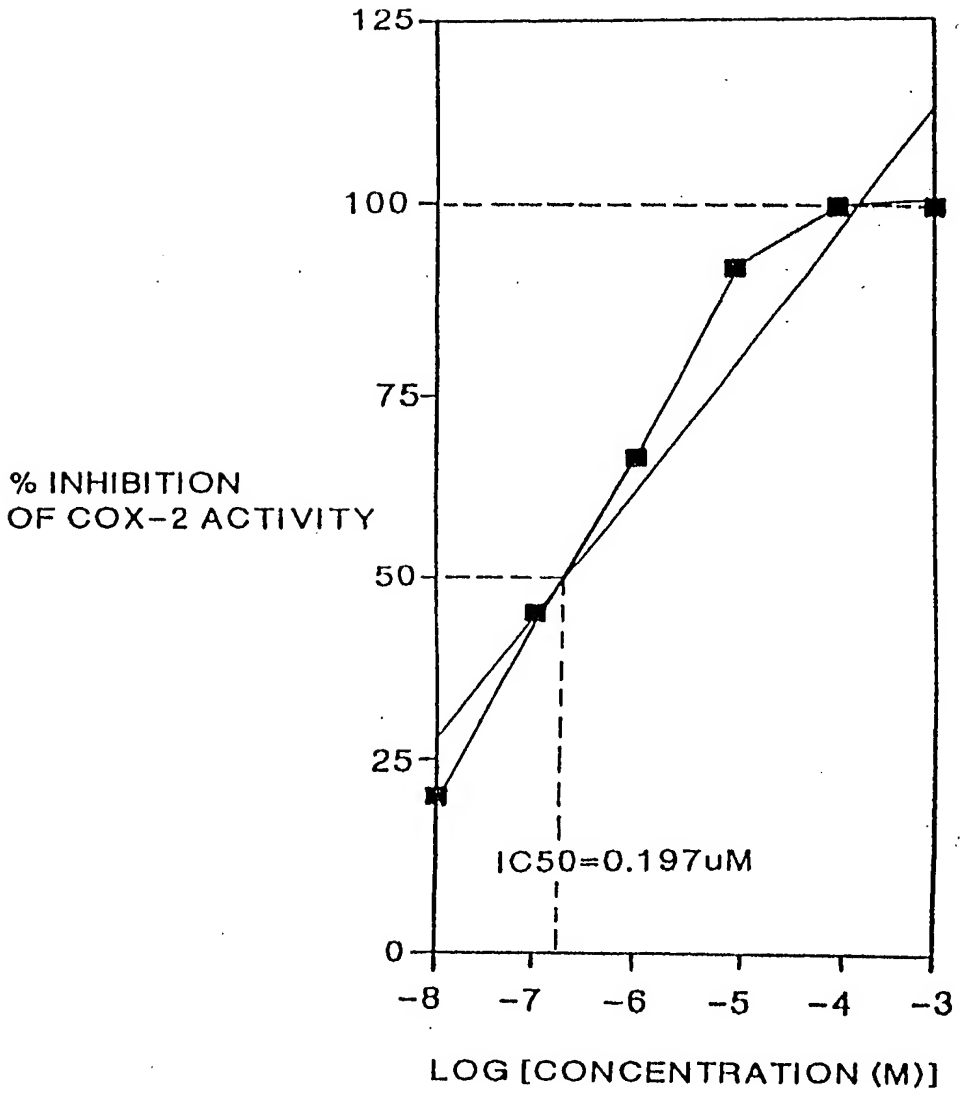

125
100
75
50
25
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=0.197uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18C

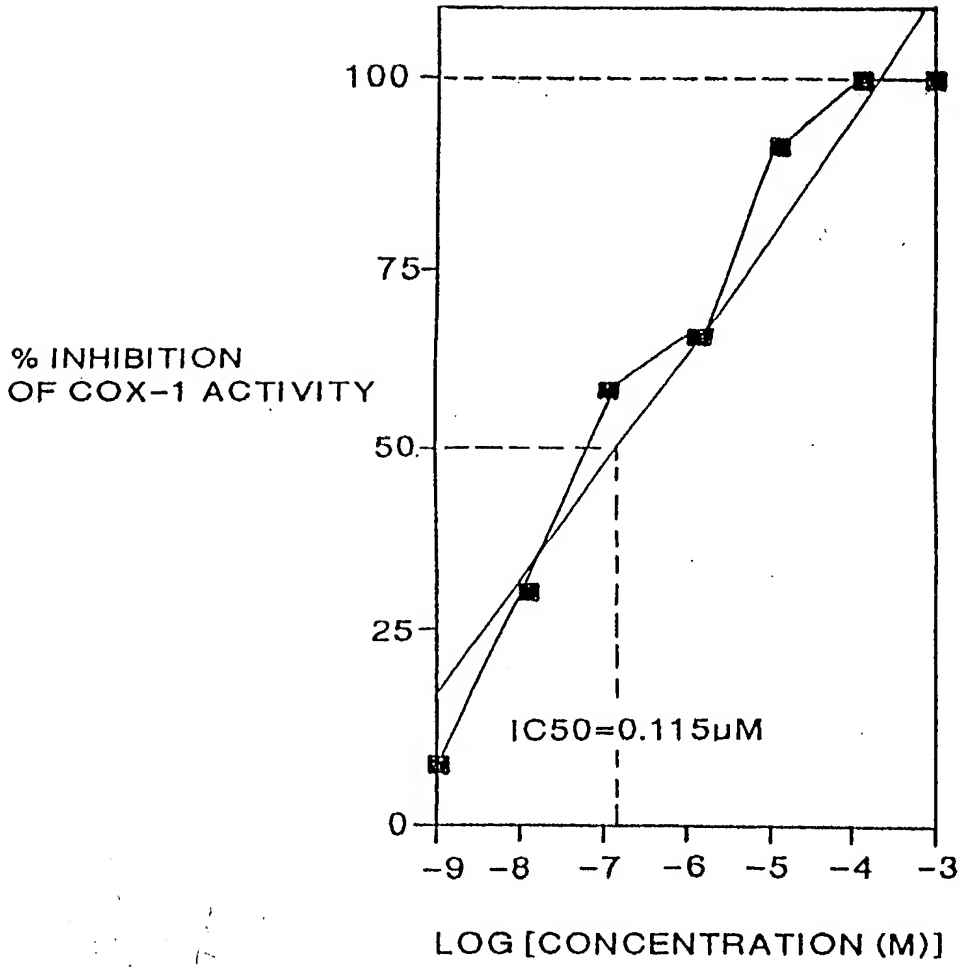

100
75
50
25
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=0.115μM
-9 -8 -7 -6 -5 -4 -3
LOG [CONCENTRATION (M)]

FIG. 18D

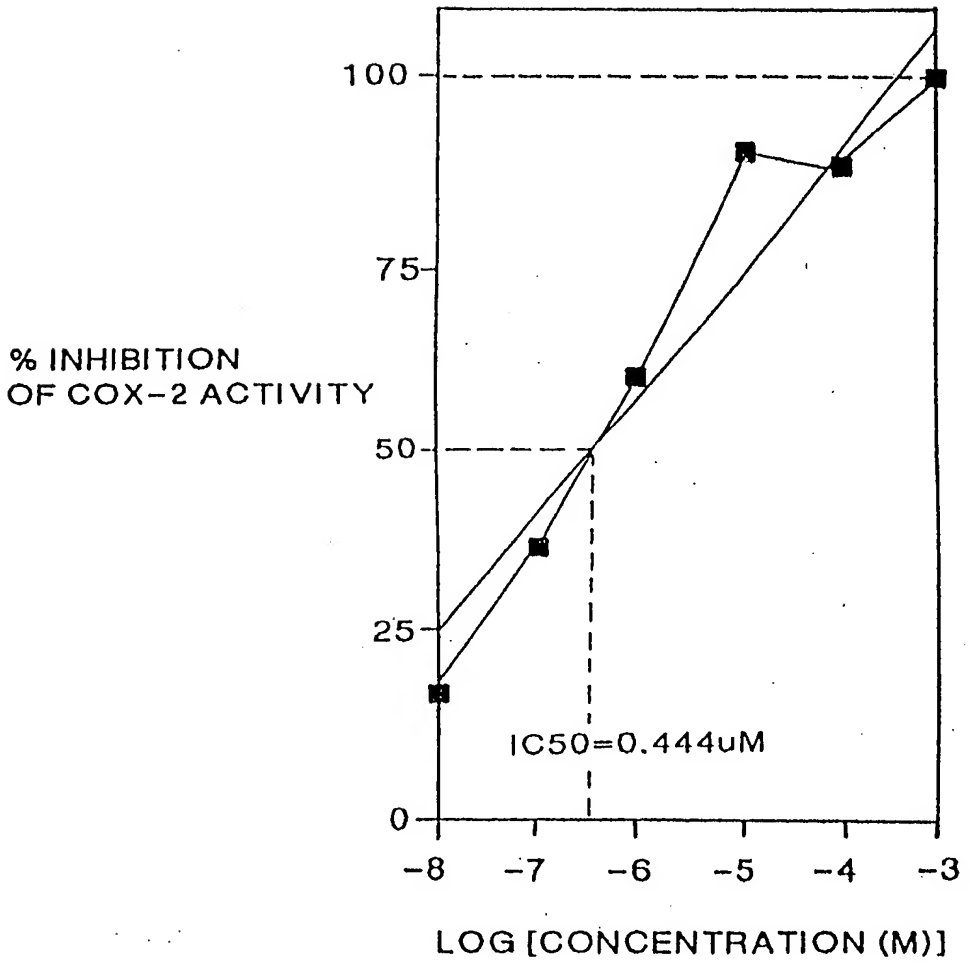

100
75
50
25
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=0.444uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18E

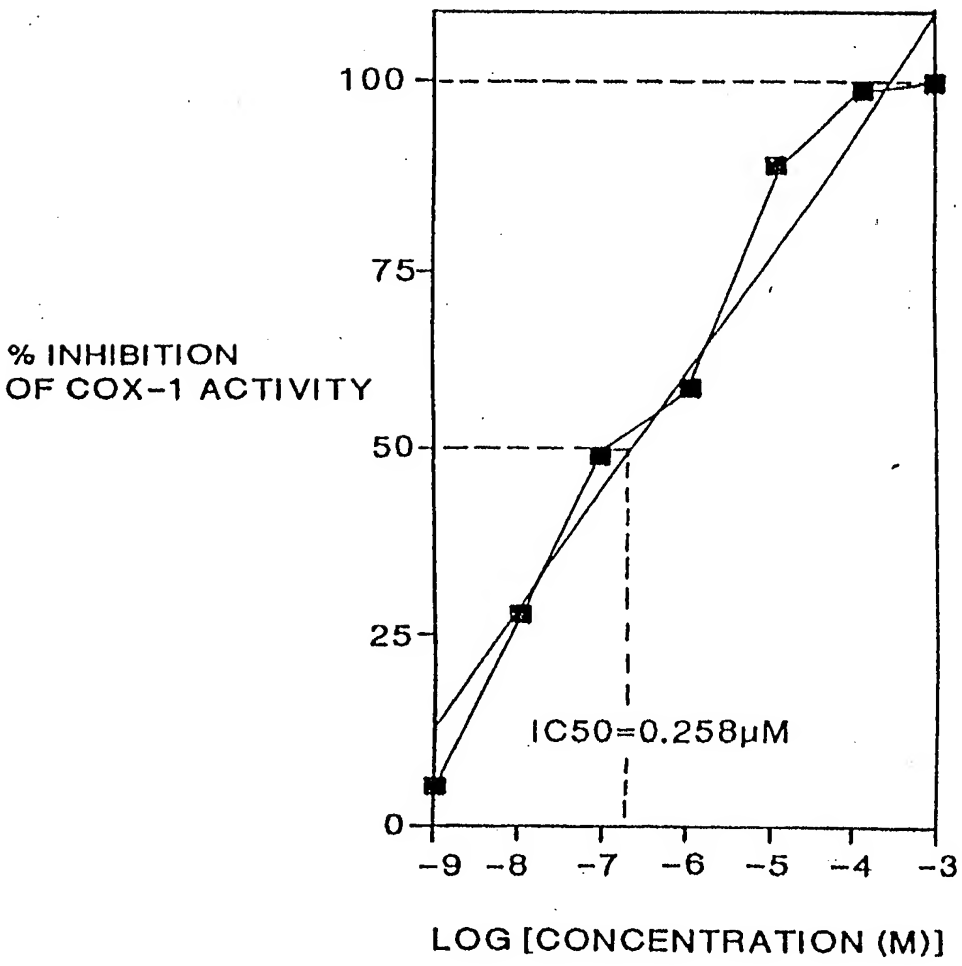

100
75
50
25
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=0.258μM
-9 -8 -7 -6 -5 -4 -3
LOG [CONCENTRATION (M)]

FIG. 18F

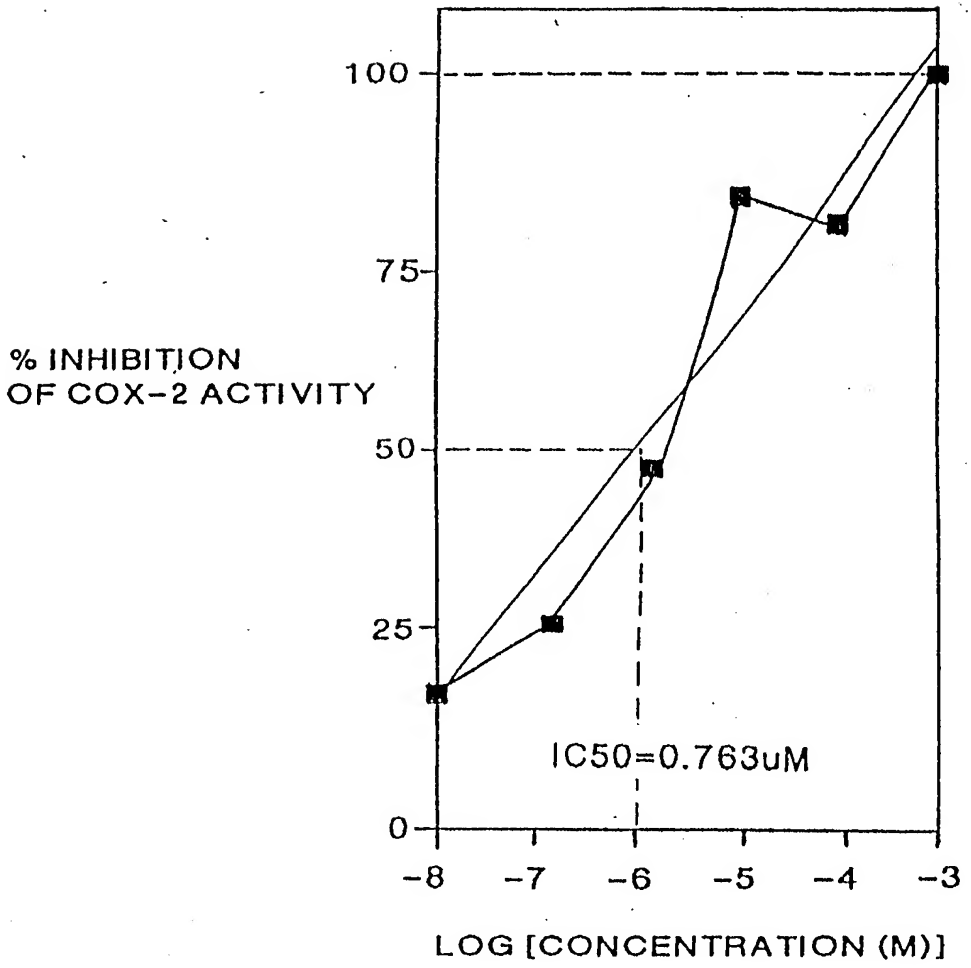

100
75
50
25
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=0.763uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18G

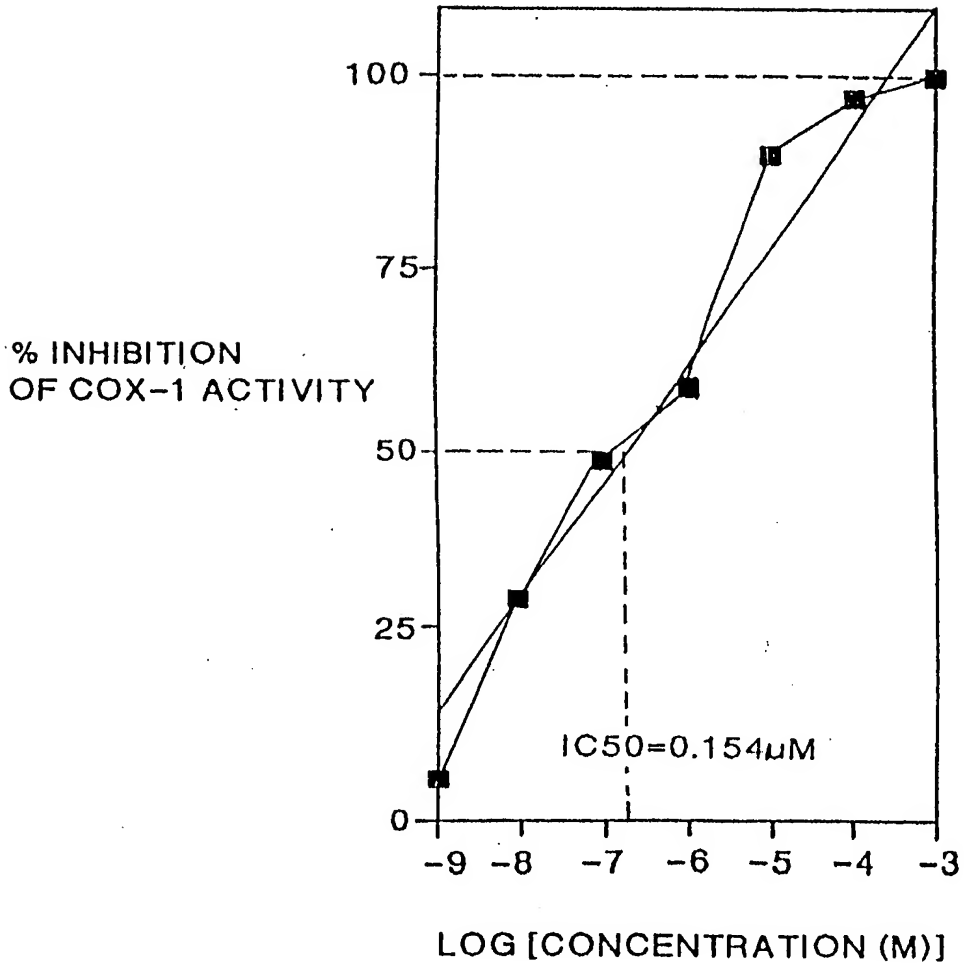

100
75
50
25
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=0.154μM
-9
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18H

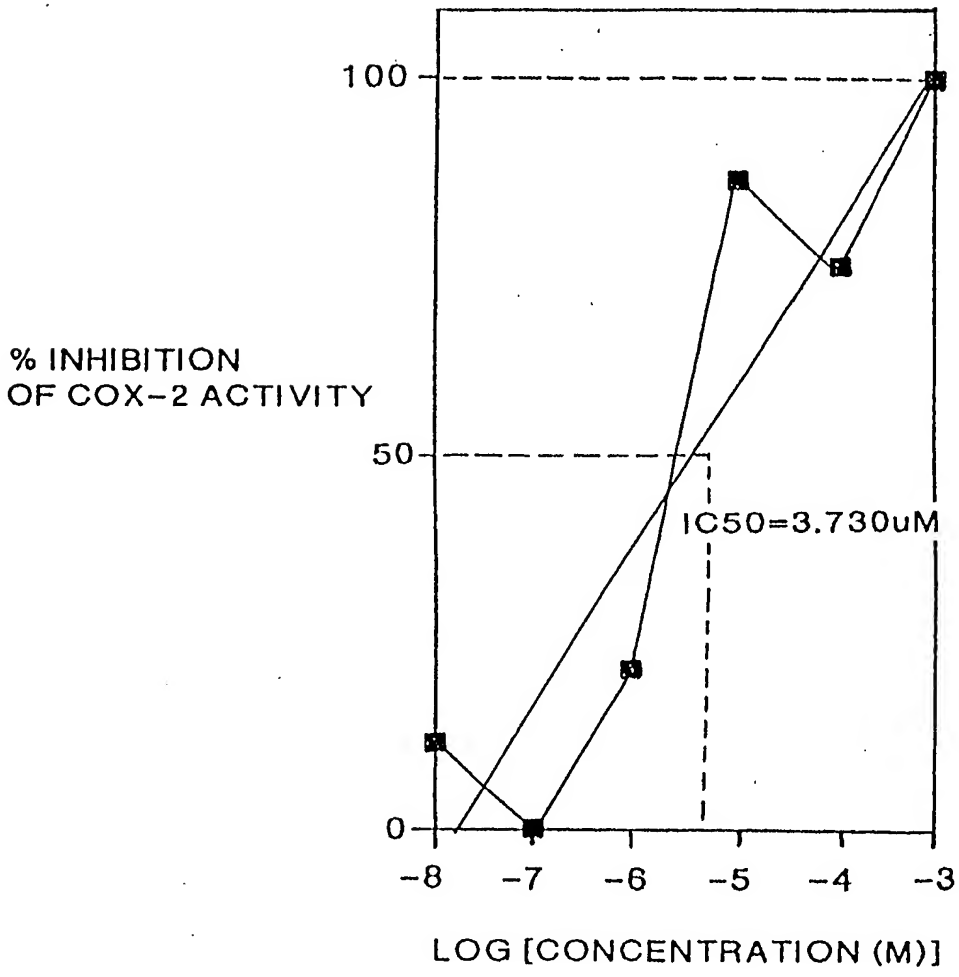

100
50
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=3.730uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18I

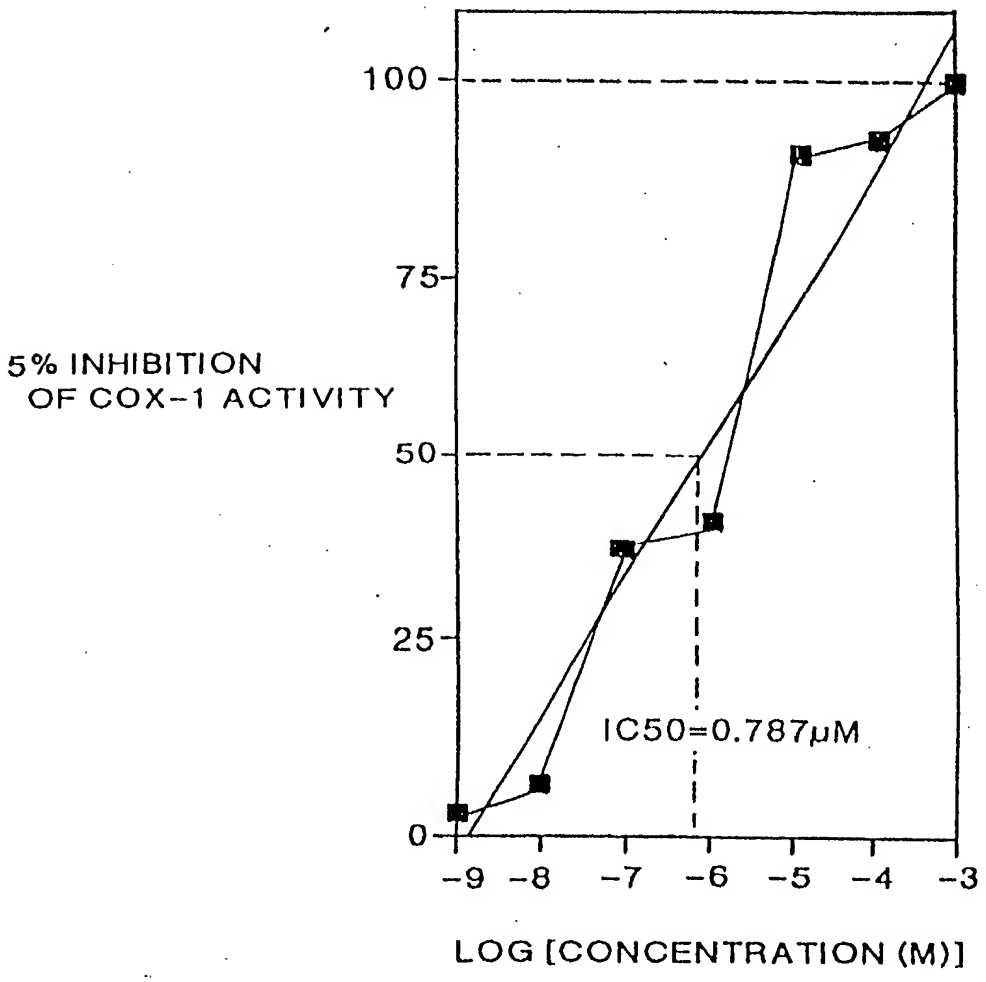

100
75
50
25
0
5% INHIBITION
OF COX-1 ACTIVITY
IC50=0.787μM
-9 -8 -7 -6 -5 -4 -3
LOG [CONCENTRATION (M)]

FIG. 18J

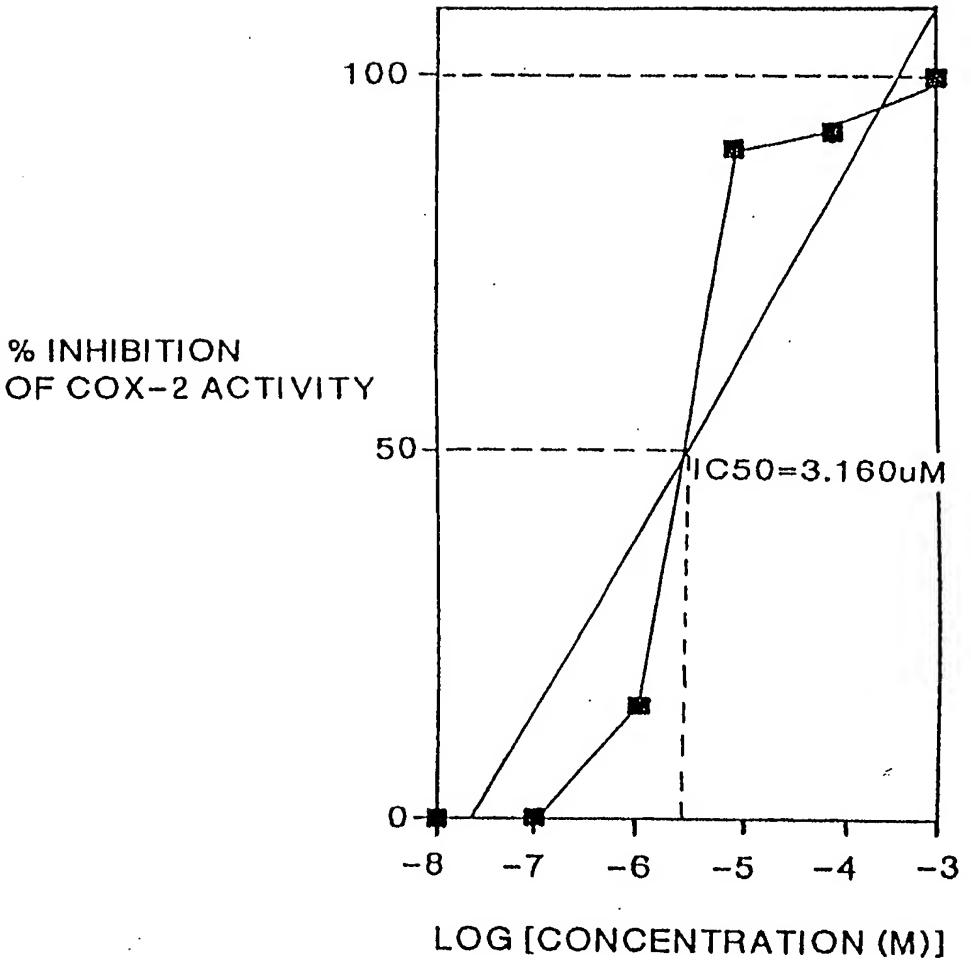

100
50
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=3.160uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18K

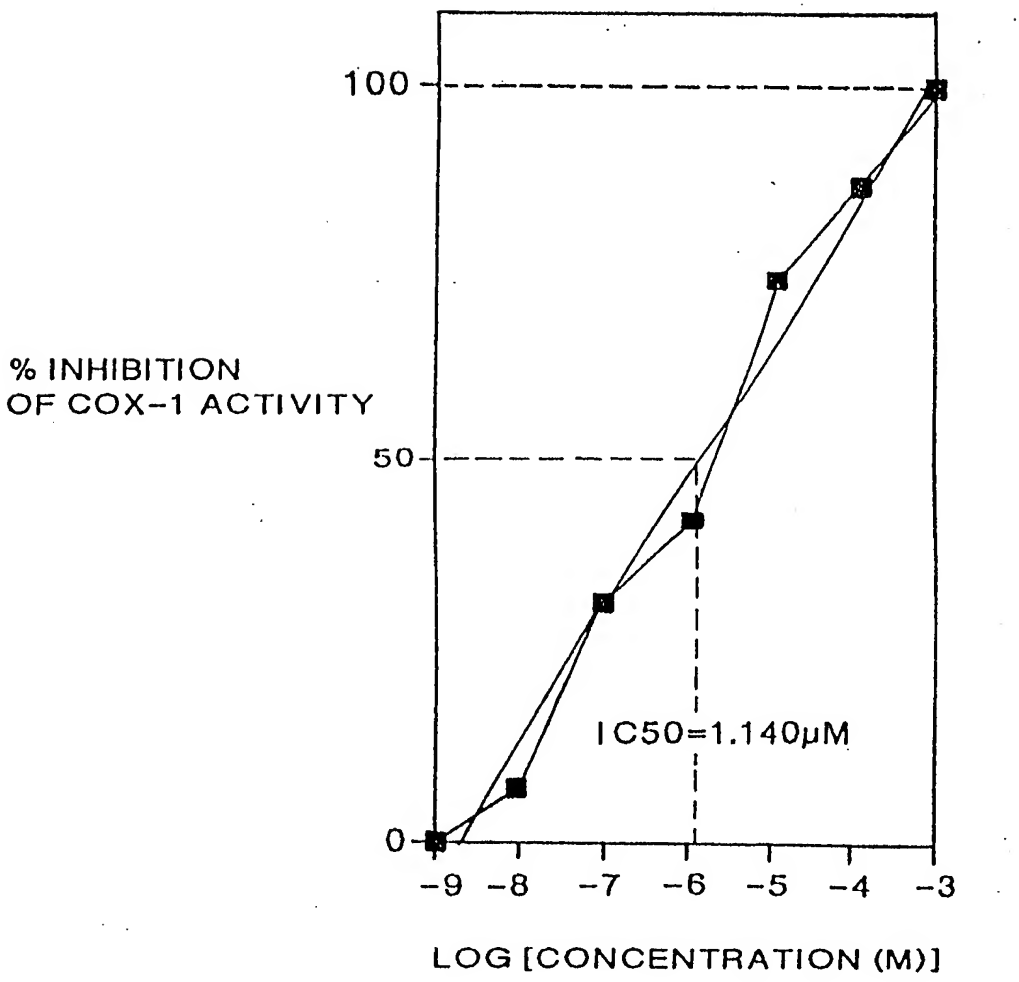

100
50
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=1.140μM
-9
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18L

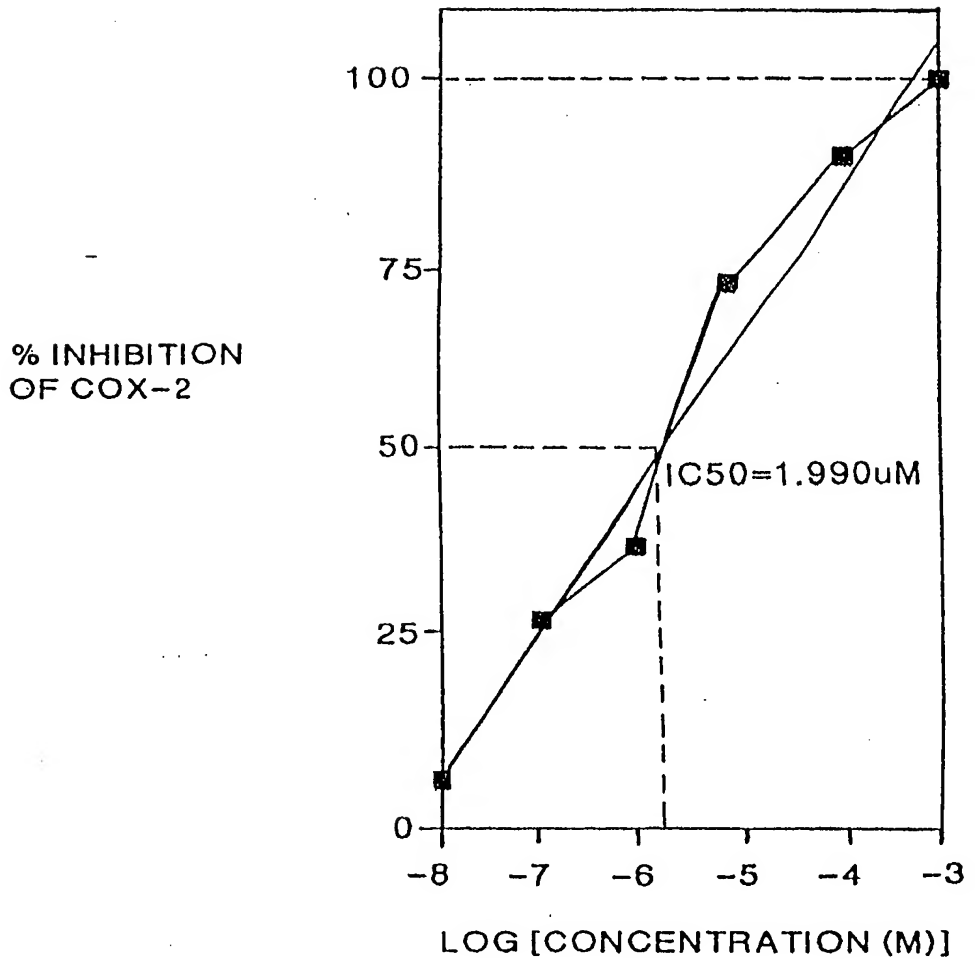

% INHIBITION
OF COX-2
100
75
50
25
0
IC50=1.990uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18M

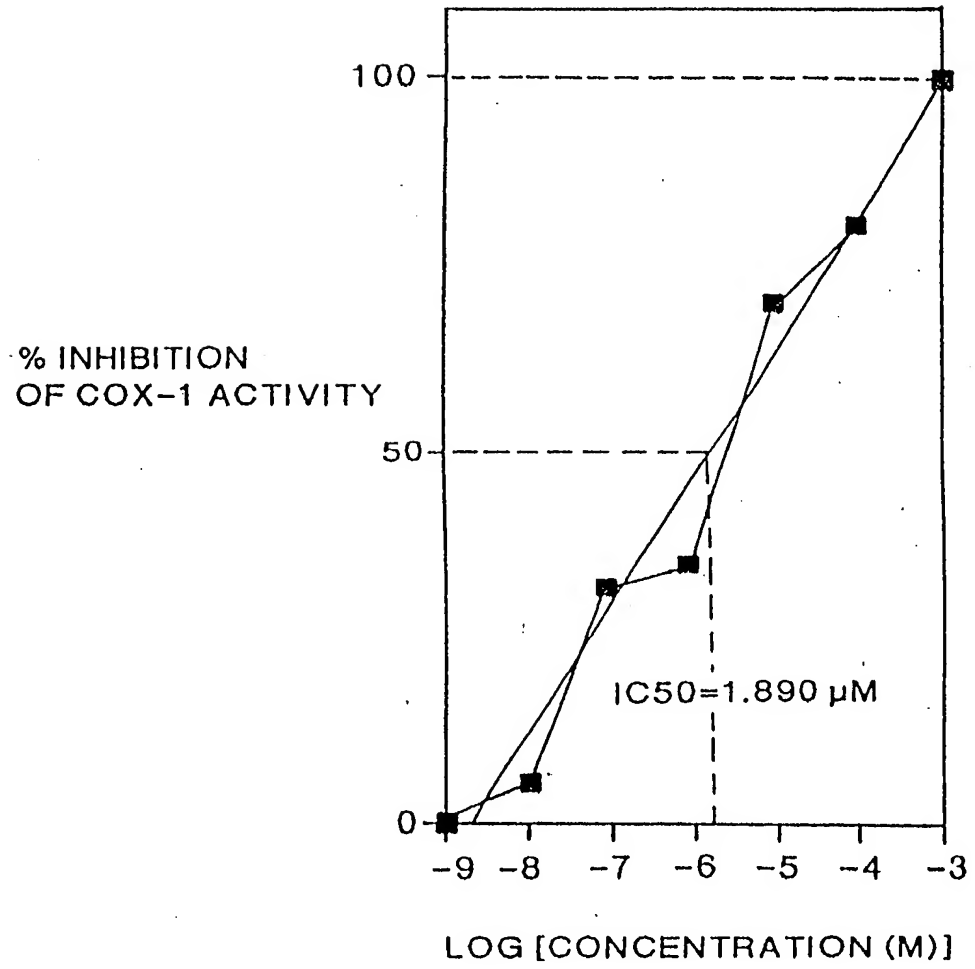

100
50
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=1.890 µM
-9
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18N

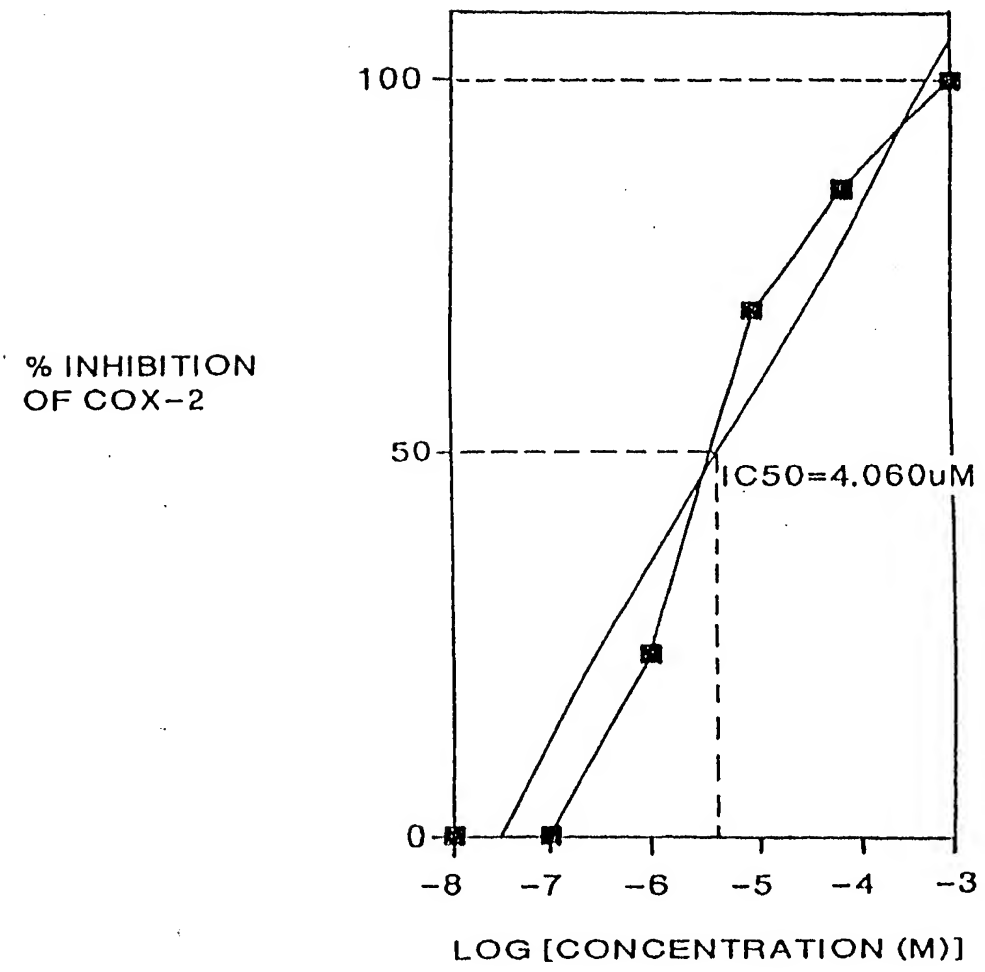

% INHIBITION OF COX-2
100
50
0
IC50=4.060uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18O

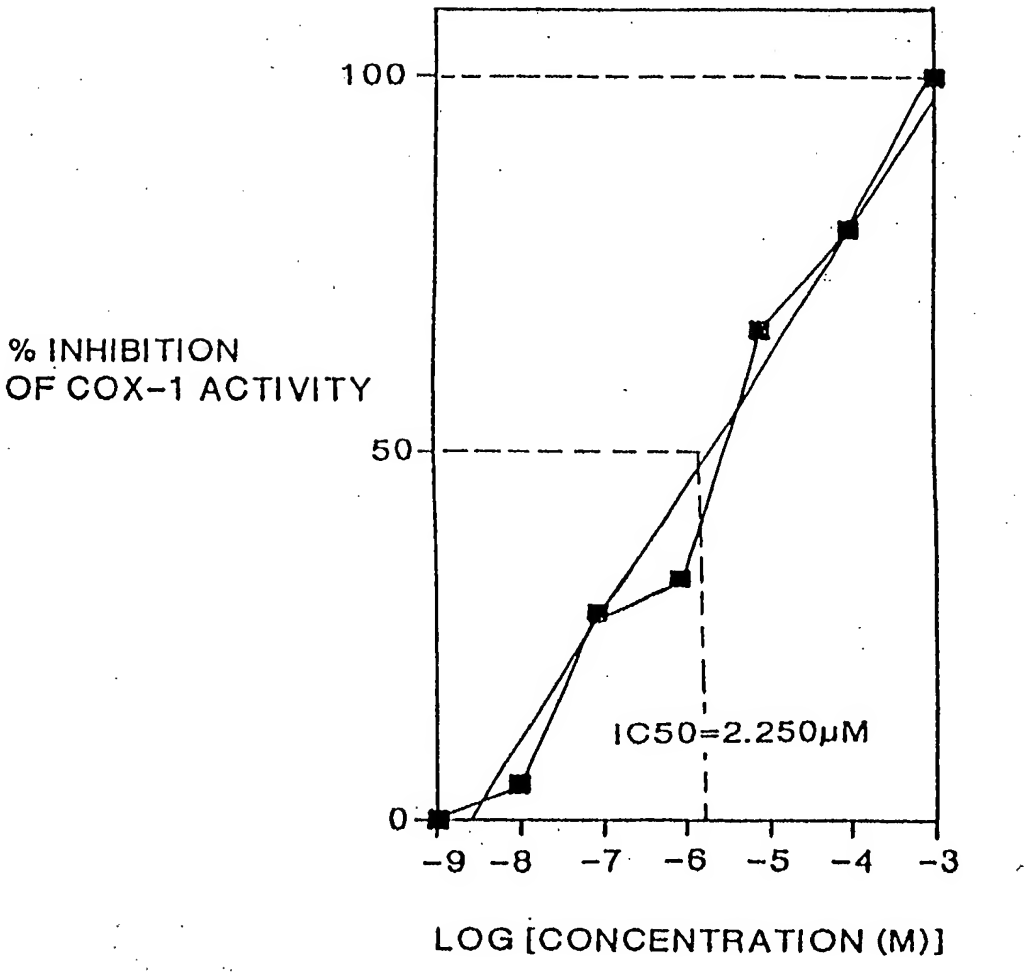

100
50
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=2.250μM
-9 -8 -7 -6 -5 -4 -3
LOG [CONCENTRATION (M)]

FIG. 18P

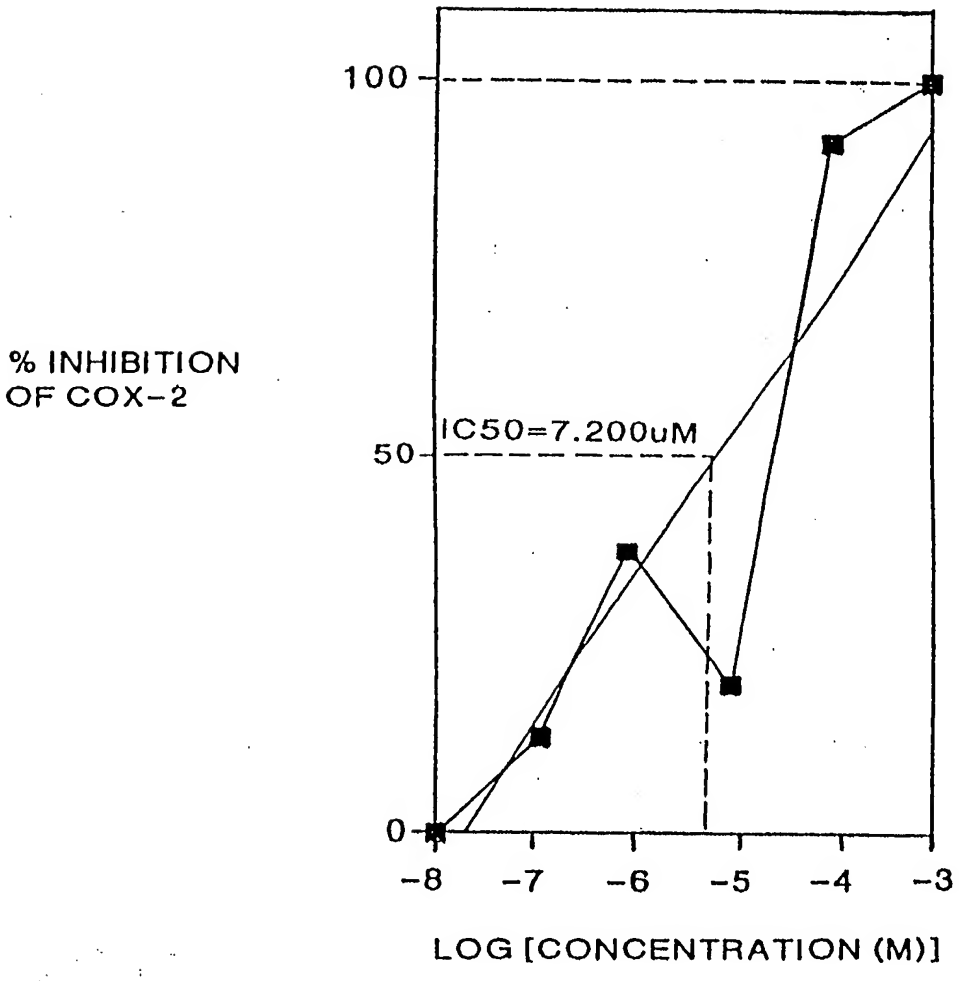

% INHIBITION
OF COX-2
100
50
0
IC50=7.200uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18Q

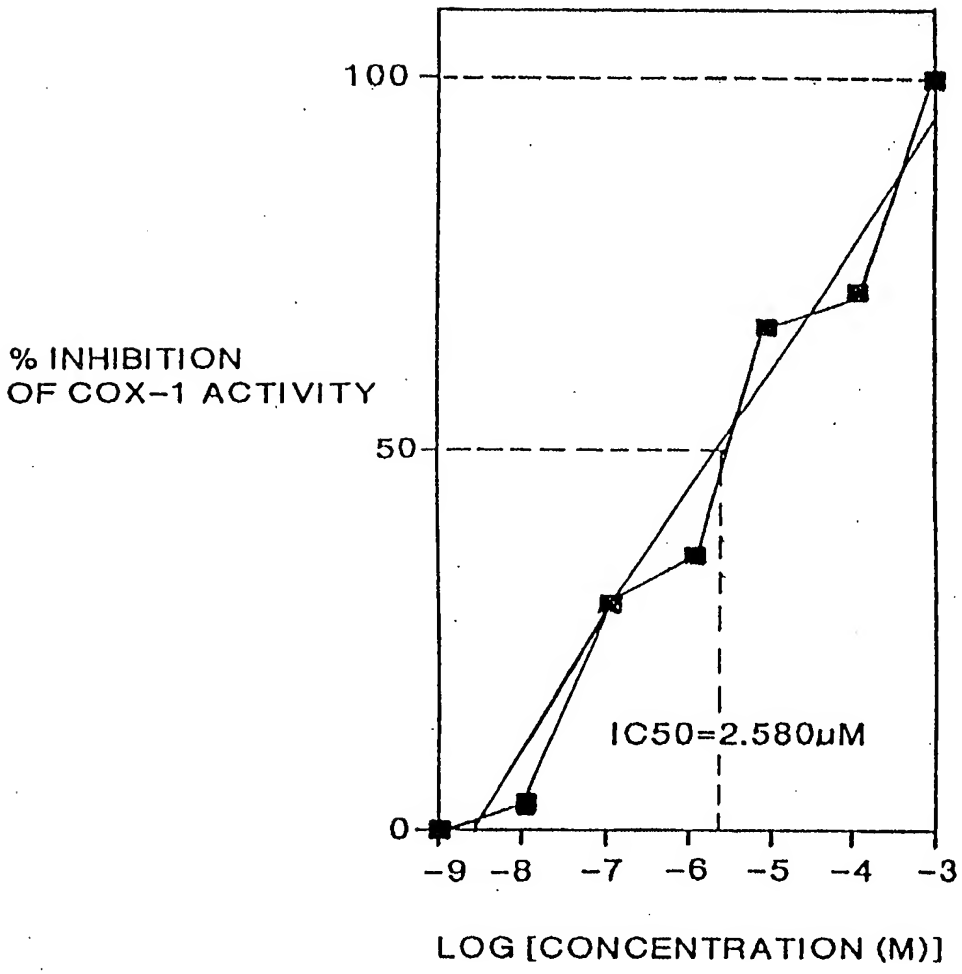

100
50
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=2.580μM
−9 −8 −7 −6 −5 −4 −3
LOG [CONCENTRATION (M)]

FIG. 18R

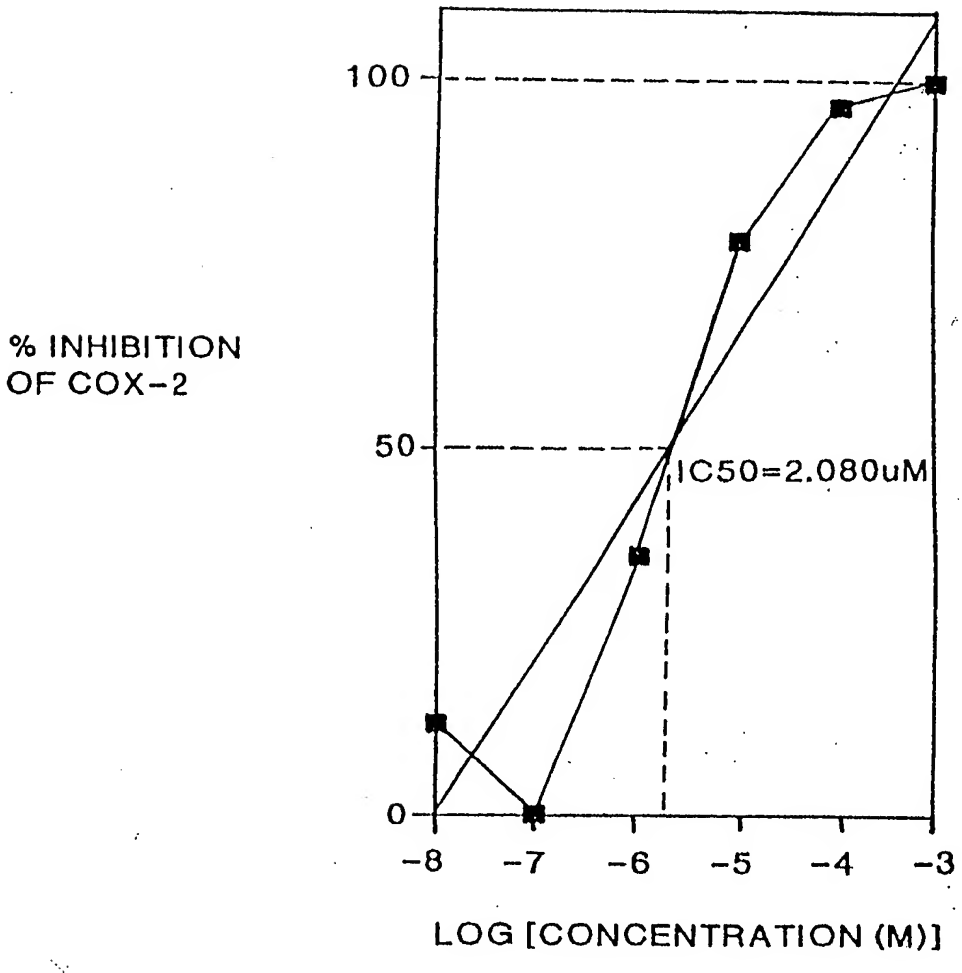

% INHIBITION
OF COX-2
100
50
0
IC50=2.080uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18S

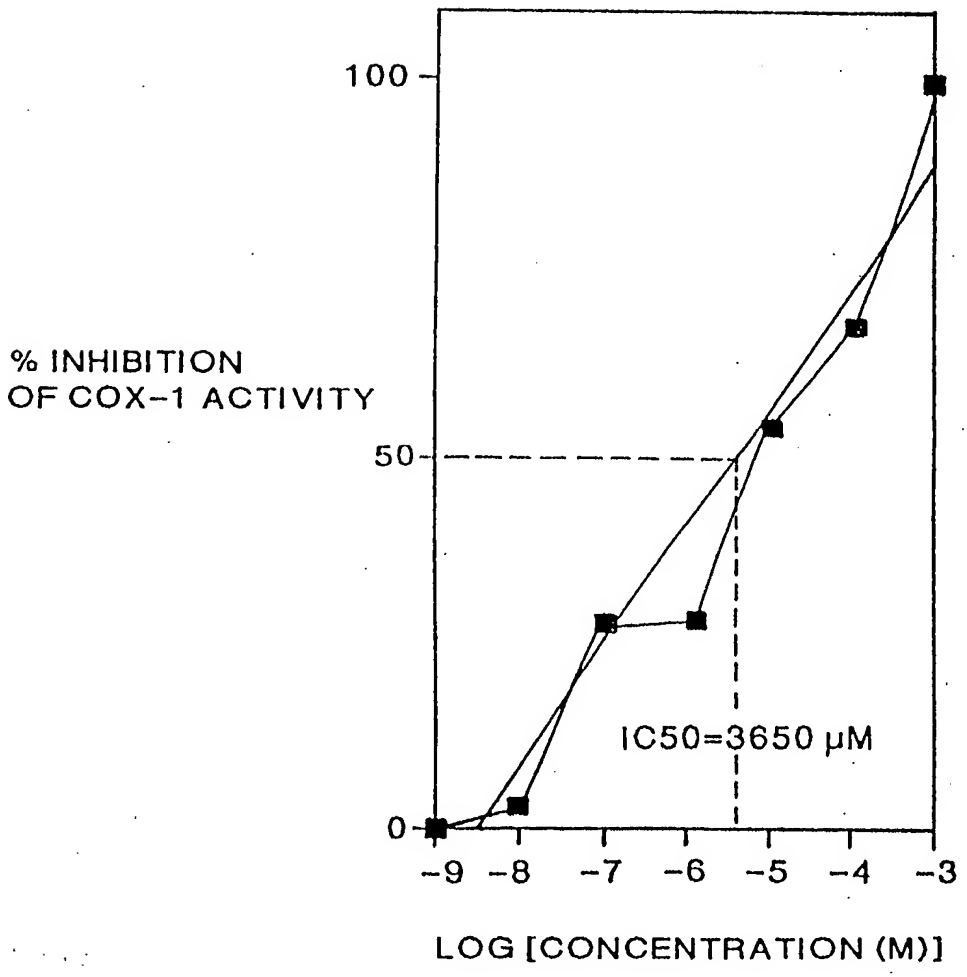

100
50
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=3650 µM
-9
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18T

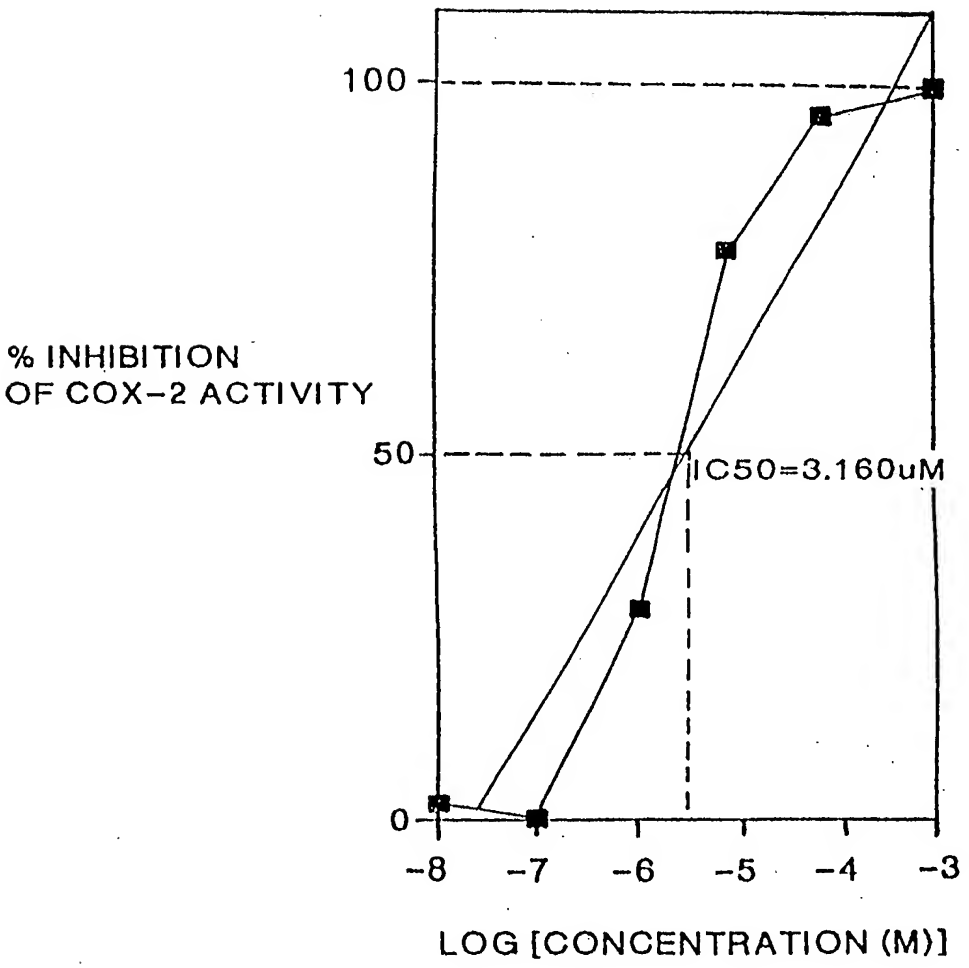

100
50
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=3.160uM
-8
-7
-6
-5
-4
-3
LOG [CONCENTRATION (M)]

FIG. 18U

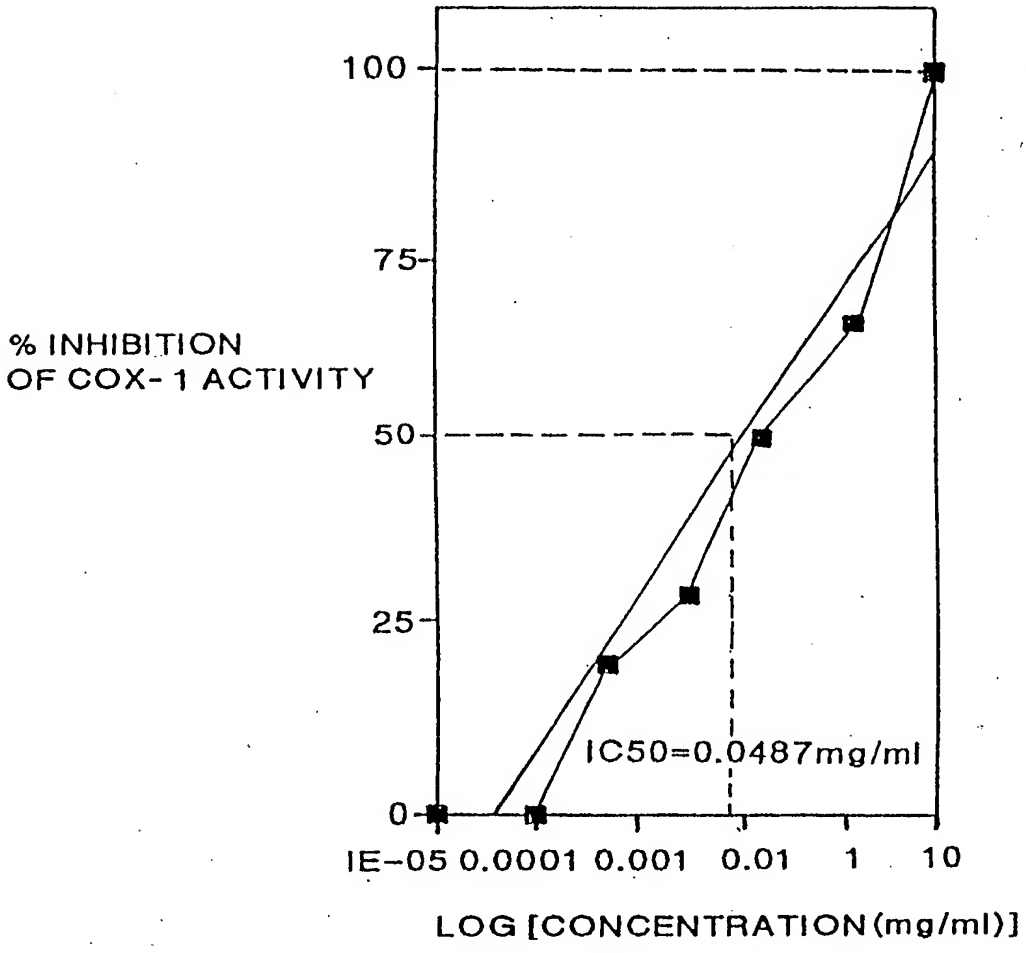

100
75
50
25
0
% INHIBITION
OF COX-1 ACTIVITY
IC50=0.0487mg/ml
1E-05 0.0001 0.001 0.01 1 10
LOG [CONCENTRATION (mg/ml)]

FIG. 18V

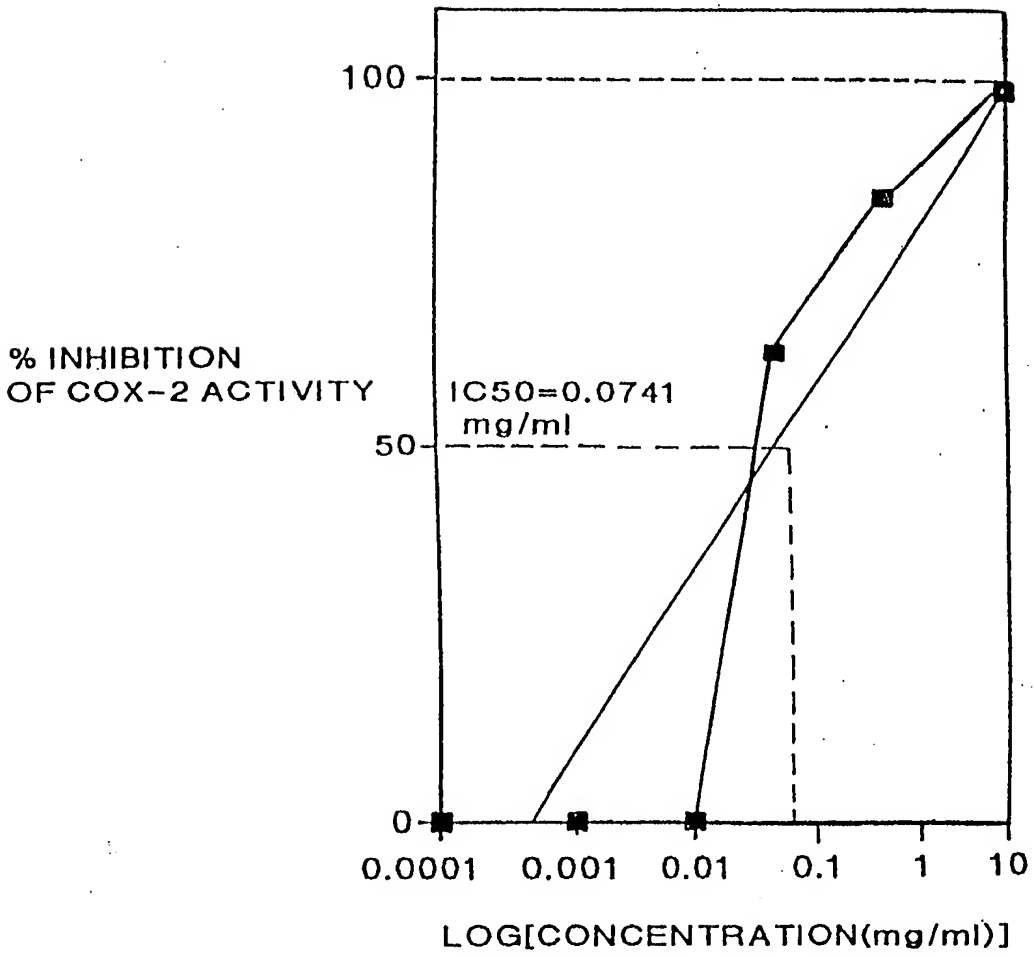

100
50
0
% INHIBITION
OF COX-2 ACTIVITY
IC50=0.0741
mg/ml
0.0001
0.001
0.01
0.1
1
10
LOG[CONCENTRATION(mg/ml)]

FIG. 19A

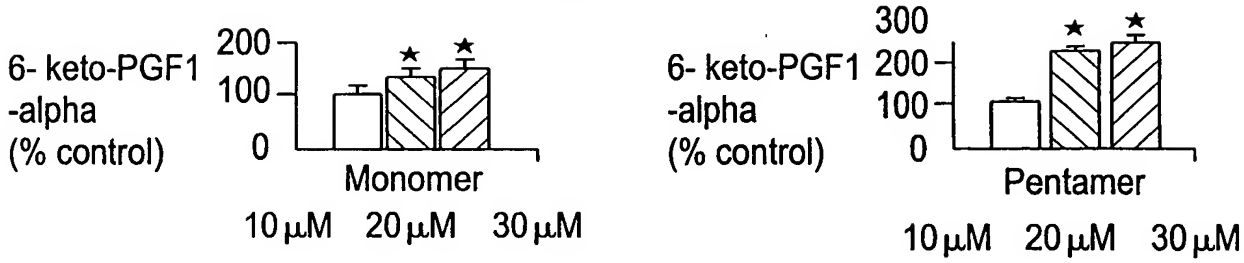


FIG. 19B

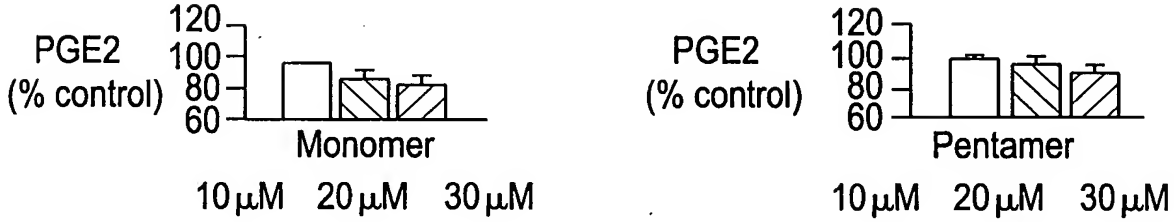


FIG. 19C

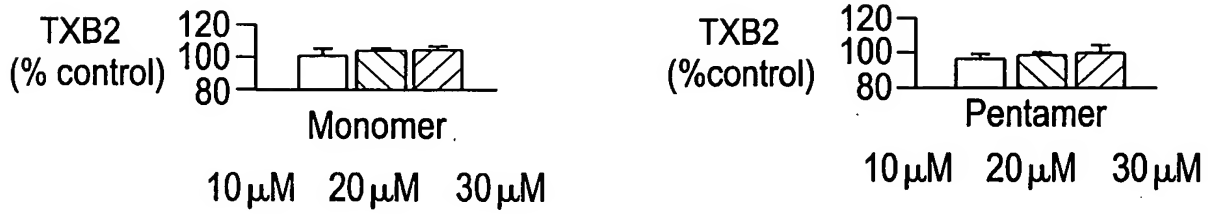


FIG. 19D

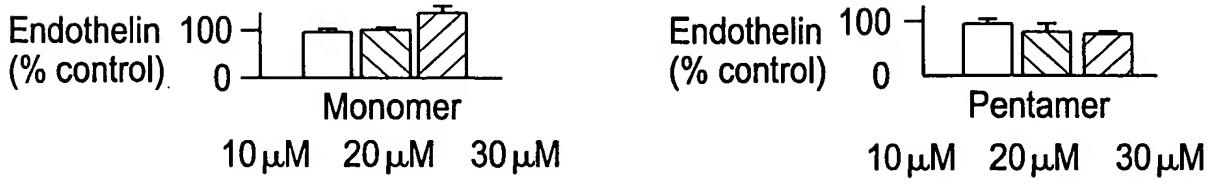


FIG. 20B

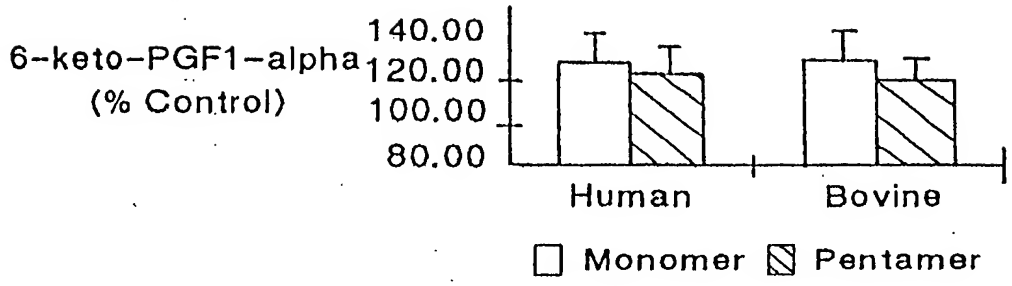


FIG. 20A

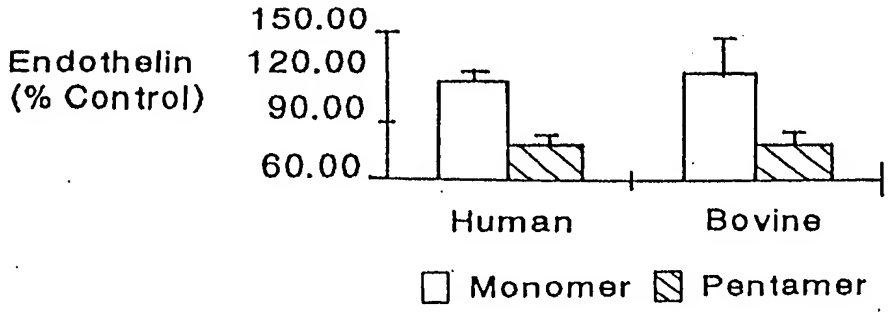


FIG. 21A

FIG. 21B

FIG. 21C

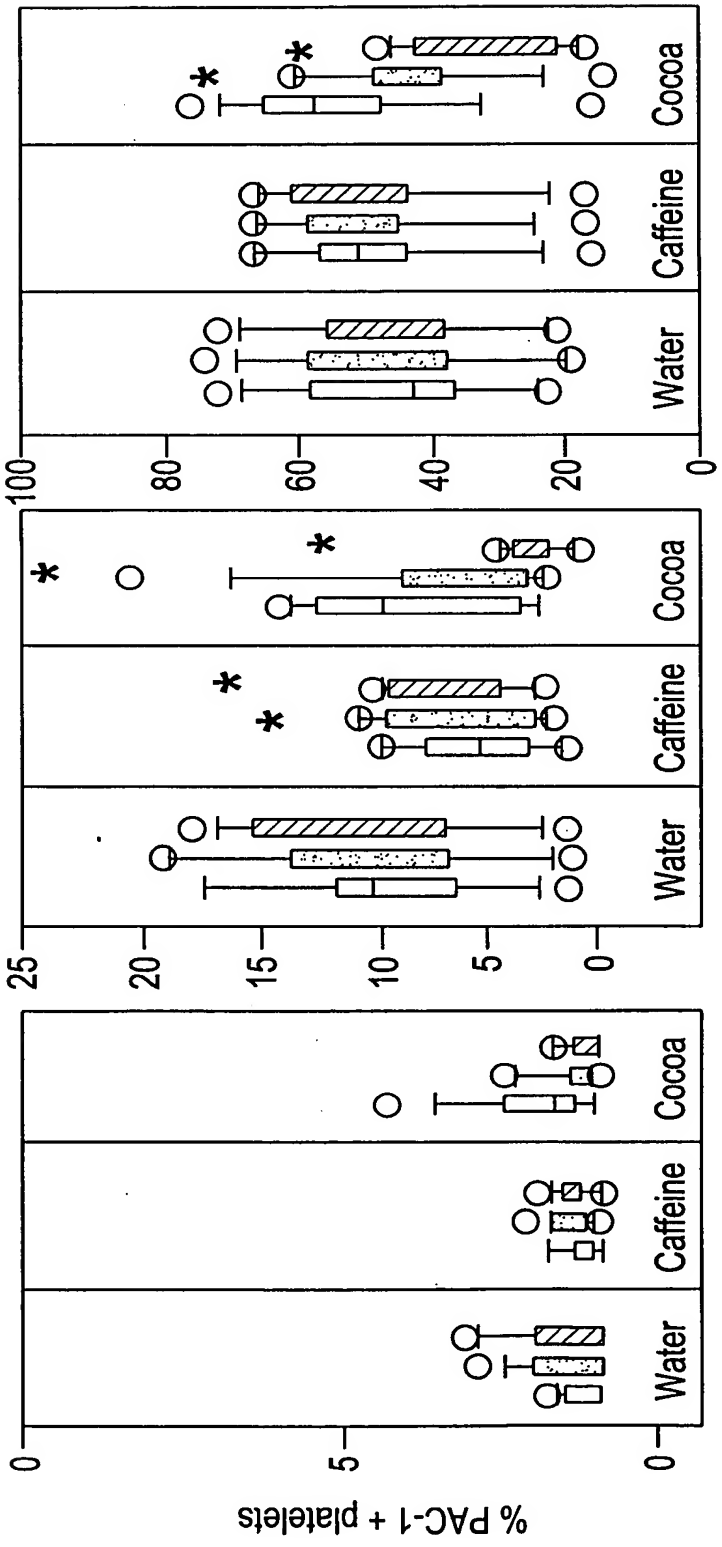


FIG. 22A

FIG. 22B

FIG. 22C